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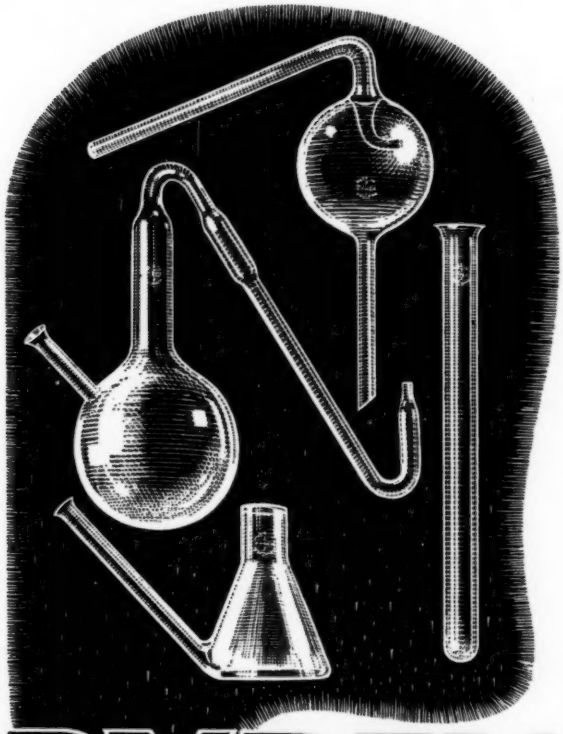

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head of the Biochemical Department of the Lister Institute and Professor of Biochemistry in the University of London in succession to his former chief, Professor Harden. In 1931 Robison was invited to deliver the Herter Lectures on Pathological Chemistry in the New York University and Bellevue Medical College, and he subsequently published the substance of these lectures in book form under the title "The Significance of Phosphoric Esters in Metabolism." The book gives in clear and simple language an excellent account of his work up to 1932. In 1933 Robison was awarded the Baly Medal of the Royal College of Physicians, an honour he greatly valued.

Robison was elected a Fellow of the Chemical Society in 1909 and served as a member of the Council from 1936—9. For some years he was a member of the Society's Publications Committee.

Those who came in contact with Robison in his daily life must have realised that few men could have shown such whole-hearted devotion and enthusiasm for their subject. The solution of a problem was its own sufficient reward. It would be difficult to imagine a more stimulating and conscientious director of a research department. Indeed his conscience sometimes diminished his effectiveness by exhausting his supply of energy and it can be said with truth that he worked unselfishly for his Department and for the Lister Institute. Robison was held in great affection by many and more especially by those younger workers who, while working at the Lister Institute, were privileged to gain his confidence. Robison had many interests beyond the realms of science and showed a strong inclination towards the arts. His interest in music, more especially in German opera and "Lieder," was sincere, and his reading of German literature, cultivated with care during his stay in Leipzig, was never allowed to lapse. He was an active gardener and found especial pleasure in this pursuit during the present difficult years.

The additional burden of Civil Defence undertaken freely and with an enthusiasm which the state of his bodily health could ill support proved too much. His colleagues and friends are left to mourn the loss of a man of rare charm and fine character; they deplore his passing and extend their sympathy to his widow and daughter who survive him.

I am indebted to the Biochemical Society for permission to reproduce parts of a more comprehensive Obituary Notice which appeared in their Journal.

W. T. J. MORGAN.

HENRY HARBEN WHITELEGG.

1916—1941.

HENRY HARBEN WHITELEGG, the only child of his parents, was educated at Denstone, and afterwards at Downing College, Cambridge. He left school somewhat earlier than the usual leaving age, and spent two years in the works of the London Midland and Scottish Railway at Crewe before entering the University, which he did at the normal age. This contact with industry was of great advantage to him in many ways, particularly in enlarging his outlook and thus giving him an exceptionally broad and sympathetic attitude towards others.

His principal subject of study was chemistry combined with physics, mineralogy, and biochemistry. As an undergraduate he rightly put his work before everything else, and graduated B.A. in 1938 with Honours in Part I of the Natural Sciences Tripos. A year later he obtained Honours in Part II of that Tripos. Although in every sense a serious student, he had numerous other interests both in the College and in the University. At Downing he was an active member of the Debating Society, and helped to start a Bridge Club which played matches with other Colleges. Although he was not strong physically, he took a keen interest in the Boat Club. The activities of Harper House for students from the Overseas Dominions enlisted his sympathetic interests.

Since the outbreak of the war he had been engaged in chemical industry, and his death at the early age of 25 years has closed the career of one who was well endowed with many of the qualities which contribute to success in this walk in life. His passing will be mourned by a large circle of friends.

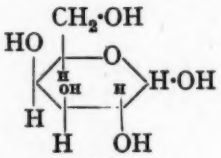
A. J. BERRY.

Recent Progress in the Chemistry of the Pectic Materials and Plant Gums.

THE TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT THE UNIVERSITY, BIRMINGHAM, ON FEBRUARY 19TH, 1940.*

By E. L. HIRST, M.A., D.Sc., F.R.S.

IT has long been considered probable that the pentose sugars arise in Nature from the corresponding hexoses by a process which involves oxidation to a uronic acid, followed by decarboxylation. It is known, for instance, that *d*-glucose and *d*-xylose are closely associated in the cellulosic constituents of plants and it is clear that *d*-xylose would be formed by the decarboxylation of *d*-glycuronic acid.



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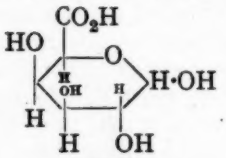

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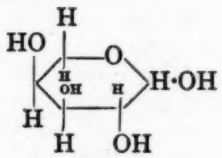


(III.)

An even more significant example is provided by the inter-relationship of galactose and arabinose, since the *l*- and not the *d*-form of arabinose would be produced by the decarboxylation of *d*-galacturonic acid (II), and it is *l*-arabinose (III) which is associated in nature with *d*-galactose (I). Relationships of this type may give an indication of the kind of mechanism involved in the formation of pentoses, but nothing is known concerning the circumstances in which this transformation takes place and no answer can as yet be returned to the question whether the xylose residues in xylan arise by oxidation and decarboxylation of the glucose residue of cellulose or whether xylan is built up by condensation of preformed xylose molecules.

Similar problems abound in connection with natural substances which contain arabinose and galactose residues as integral parts of the molecule. In no instance is there direct evidence concerning the mode of origin of the pentose and this lecture is concerned mainly with a discussion of the problem in the light of results obtained by an indirect method of approach. That the obvious explanation must be regarded with caution is well illustrated by the case of xylan already cited. Here the position is complicated and the simple hypothesis of direct derivation from cellulose has been rendered uncertain by recent work which has established the presence of *l*-arabofuranose as terminal end groups in the xylan molecule (Haworth, Hirst, and Oliver, J., 1934, 1917).

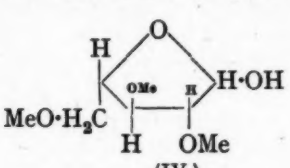
In order to gain further information concerning the inter-relationship of pentoses and hexoses, workers in the Bristol University laboratories are examining the structure of hexose and pentose residues associated with one another in certain polysaccharides of plant origin. The groups of natural products which afford special opportunities for this type of investigation are the pectic substances, the plant gums, and the plant mucilages. Members of each of these groups afford favourable conditions for comparing the ring structure and mode of linkage of the arabinose, galactose, and galacturonic acid residues present in the molecule, and, as will appear in what follows, the somewhat unexpected conclusion has been reached that in none of the substances investigated is it possible for the arabinose to arise intramolecularly from the associated galacturonic acid or from the associated galactose residues. Furthermore, the galactan which is associated with the pectin complex cannot, by oxidation at C_6, give rise to the galacturonic acid residues present in pectic acid, unless by way of hydrolysis and subsequent re-synthesis. Furthermore, it is clear that the araban which accompanies pectic acid in the pectin complex cannot be formed directly by decarboxylation of the pectic acid chains. It seems, therefore, that the natural processes involve hydrolysis of one polysaccharide, transformation of the resulting hexose into the corresponding uronic acid or pentose, and lastly, synthesis of another polysaccharide from the uronic acid or pentose so formed. Some further details of the evidence upon which these conclusions are based will now be given.

Pectic Substances.—It has long been known that " pectin " consists essentially of a mixture of polysaccharides, including an araban, a galactan, and a polygalacturonide (pectic acid). These three are present in most (or perhaps all) pectic substances, but their relative proportions vary widely with the

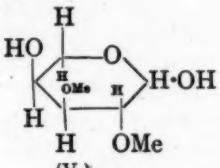
* The preparation of this lecture for publication was unavoidably delayed and the account now presented has been compiled in collaboration with Dr. J. K. N. Jones, to whom I wish to express my best thanks. The opportunity has been taken to render the survey more complete by the inclusion of references to some recent work, notably that of Dr. F. Smith on gum arabic, the full details of which became available after the date on which the lecture was delivered. E. L. H.

origin of the pectin. Advantage has been taken of this in a preliminary survey of the subject, in that different pectic substances can be utilised as convenient sources for the various components. For instance, a convenient source of araban was found in the peanut, from which, after removal of the oil, protein, and other materials, a crude pentosan was isolated. After further purification, this was found to contain neither galactose nor galacturonic acid residues, and on hydrolysis with 0·01N-acid it gave rise to *l*-arabinose only. This ease of hydrolysis indicated that the polysaccharide was built up of arabofuranose molecules. The araban, after methylation by treatment with thallous hydroxide and methyl iodide, was transformed into the fully methylated derivative, which has a high negative rotation indicating α-linkages.

It was then shown that arabans from peanut, apple, and citrus pectins had very similar properties and after methylation they gave similar methyl derivatives which yielded on hydrolysis equimolecular proportions of 2 : 3 : 5-trimethyl *l*-arabinose (IV), 2 : 3-dimethyl *l*-arabinose (V) and a monomethyl *l*-arabinose which is probably the 3-derivative (VI). The dimethyl and monomethyl arabinoses are isolated as pyranose sugars, but in the unhydrolysed araban the corresponding residues are present in the furanose form. The absence of a methyl group at C_5 permits ring change after hydrolysis. These observations demonstrate the presence of branch chains in the araban molecule and one of the possible structural formulæ is typified in (VII). At present a decision cannot be made between (VII) and its obvious variants, but the general type of structure is apparent (Hirst and Jones, J., 1938, 496; 1939, 452, 454; Beaven, Hirst, and Jones, J., 1939, 1865).



(IV.)



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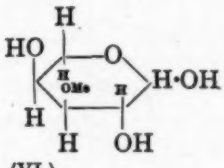

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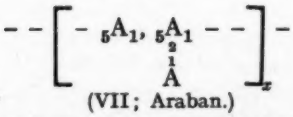
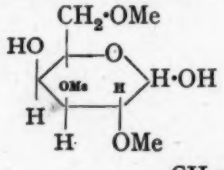


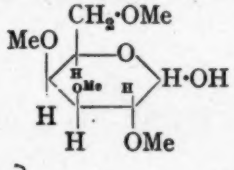
A = α-arabofuranose residue united to other residues through the numbered C-atoms.

(VII; Araban.)

The isolation in the pure state of the galactan portion of a pectin has been achieved, up to the present, in one case only, namely, from the seeds of *lupinus albus*, which are a rich source of the polysaccharide (Schulze and Steiger, *Ber.*, 1887, **20**, 290). We are indebted to Professor Skene, of the University of Bristol, for drawing our attention to the possibilities afforded by this material, in which the galactan occurs, together with smaller quantities of araban and pectic acid. The araban was first removed by hydrolysis with 0·01N-acid, and the pectic acid was precipitated as its insoluble calcium salt. The residual polysaccharide showed a low positive rotation and was hydrolysed, giving *d*-galactose, at a rate which indicated a pyranose structure. On methylation, this polysaccharide gave a trimethyl galactan, hydrolysis of which yielded 2 : 3 : 6-trimethyl *d*-galactose (VIII), accompanied by a small quantity of 2 : 3 : 4 : 6-tetramethyl *d*-galactose (IX). The polysaccharide (X) consisted, therefore, of a chain of β-*d*-galactose units linked through the 1- and 4-positions and it could not, on oxidation and decarboxylation, give rise to an araban with furanose ring structure [compare (VII)] without intermediate hydrolysis, followed by re-synthesis (Hirst, Jones, and Walder, unpublished results).

(VIII.)





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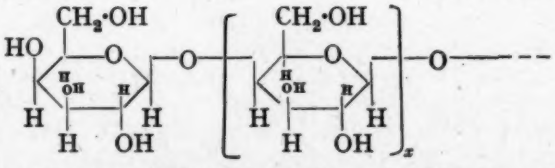


(X; Galactan.)

A small quantity of crude araban was isolated from the seeds of *lupinus albus* by extraction with 70% alcohol. It had a high negative rotation and after methylation and hydrolysis gave a mixture of sugars,

among which 2 : 3 : 5-trimethyl (IV) and 2 : 3-dimethyl *l*-arabinose (V) could be detected. It was evident that this araban was very similar to, if not identical with, the araban isolated from peanut, apple, and citrus pectins.

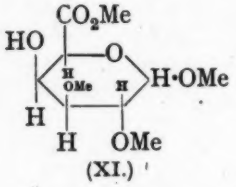
The pectic acid component of pectin was isolated in a nearly pure state from white lupin seeds (which provided a source from which all the three main components were isolated) and from apple, citrus, peanut and hawthorn pectins, by precipitation as the copper and calcium salts, followed by purification of the free acid (Beaven, Hirst, Jones, and Walder, unpublished results). It is difficult to remove the last traces of water, ash, and associated araban and galactan, but the purest samples isolated had equivalent weights close to 176, high positive rotations ($[\alpha]_D$ + 170° to + 230°) and after hydrolysis no substance other than *d*-galacturonic acid could be detected. Owing mainly to difficulties connected with the viscosity of alkaline solutions of the pectic acid, methylation proceeded unsatisfactorily, and for preliminary structural work a degraded pectic acid ester was prepared by boiling the pectic acid for some time with methyl-alcoholic hydrogen chloride. This treatment served to remove ash, adsorbed galactan and araban, caused partial hydrolysis of the polysaccharide, and esterification of the carboxyl group (Morrell, Baur, and Link, *J. Biol. Chem.*, 1934, **105**, 1).

TABLE I.

Source.	Equiv. wt.	Specific rotation.	Methoxyl, %.	Barium salt. Ba, %.	Barium salt. OMe, %.
Strawberry	200	—	17·4	25·2	1·8
Raspberry	187	+197°	15·7	25·1	0·8
Apple	195	+229	17·4	24·6	1·5
Citrus	215	+212	13·8	26·8	1·3
Lupinus albus	210	+170	17·9	—	—
Required for a methyl poly-galacturonide methyl ester containing eight units :				27·7	1·6

By this means degraded polyesters were prepared from citrus, apple, raspberry, strawberry, and *lupinus albus* pectic acids (see Table I) (Beaven, Hirst, Jones, and Walder, unpublished results). Methylation of these with thallous hydroxide and methyl iodide gave a trimethyl derivative, which underwent hydrolysis only with extreme difficulty. Hydrolysis in a sealed tube with methyl-alcoholic hydrogen chloride at an elevated temperature gave the methyl ester of 2 : 3-dimethyl methyl-*d*-galacturonoside (XI), the structure of which was proved by oxidation with bromine water, followed by esterification, giving the 1 : 4-lactone of 2 : 3-dimethyl mucic ester (XII), which with periodic acid gave *l*-dimethoxysuccinic acid (XIII), after oxidation of the aldehyde with bromine water. This result, taken in conjunction with the extraordinarily high stability of pectic acid to acidic reagents and its high positive rotation (over + 200°), indicates that in the pectic acid molecule there is present a series of pyranose α-galacturonic acid residues mutually linked through positions 1 and 4 (XIV) (Beaven and Jones, *Chem. and Ind.*, 1939, **58**, 363).

Simultaneously with this work the direct methylation of pectolic acid derived from citrus pectin was carried out by Smith at the University of Birmingham (*Chem. and Ind.*, 1939, **58**, 363; J., 1940, 1106, 1506). On hydrolysis of the methylated derivative, only 2 : 3-dimethyl galacturonic acid was obtained, which was proved by oxidation to be the 1 : 4-lactone of 2 : 3-dimethyl mucic ester (XII), identical with material obtained by synthesis. Although the dimethyl galacturonic acid was isolated after the methanolysis as the furanose form of the methylgalacturonoside, Smith's views concerning the pyranose ring of the uronic acid residues in pectin are in agreement with those indicated above, the transformation to the furanose ring form taking place after hydrolysis of the pectic acid (Luckett and Smith, J., 1940, 1506).



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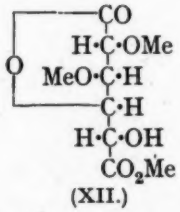
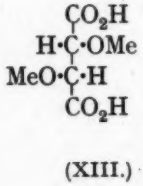


(XII.)

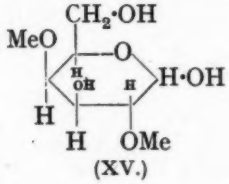


(XIII.)

(XIV; Pectic acid.)

If (XIV) represents the type of structure present in pectic acid, it is clear that the latter cannot be derived from the accompanying galactan (X) by oxidation of the primary alcoholic grouping at C_6 to a carboxyl group, since in (X) the repeating units are β-*d*-galactopyranose residues whereas in pectic acid the repeating units are present in the α-form. So far as present knowledge goes, it would be necessary for hydrolysis and re-synthesis to take place if the galactan were to be the forerunner of pectic acid in the plant.

Further evidence in favour of the hypothesis that hydrolysis, followed by re-synthesis, occurs during the transformation of certain hexosans into the corresponding pentosans, has been obtained from a study of the so-called ε-galactan or galacto-araban of larchwood (Schorger and Smith, *Ind. Eng. Chem.*, 1916, **8**, 494). This has been shown to be a mixture of araban and galactan and there is evidence that the araban consists of arabofuranose units whereas the galactan portion is composed of galactopyranose units. This galactan, on methylation, followed by hydrolysis, gives rise to equimolecular proportions of tetramethyl *d*-galactopyranose, 2 : 4-dimethyl *d*-galactopyranose (XV), and a trimethyl *d*-galactopyranose, the constitution of which has not yet been established with certainty [it may be 2 : 3 : 4- (XVI) or 2 : 4 : 6-trimethyl galactose (XVII)]. It follows, therefore, that the galactan is of the branch chain type (XVIII is one of the possible formulæ) and is very different from the galactan present in pectins. Furthermore, it is impossible for the galactan to give the araban by oxidation and decarboxylation without intermediate hydrolysis, since (*d*-galacto)pyranose units are present in one and (*l*-arabo)-furanose units in the other (Campbell, Hirst, and Jones, *Nature*, 1941, **147**, 25). At present, therefore, little definite can be said regarding the inter-relationship of galactans, polygalacturonides and arabans, apart from the fact that *d*-galactose, which gives rise to *l*-arabinose, is almost invariably associated in natural products with *l*-arabinose and is probably its precursor.



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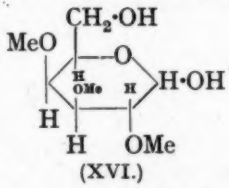

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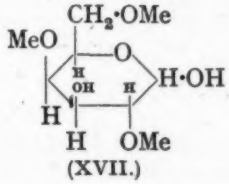

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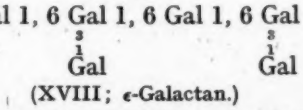
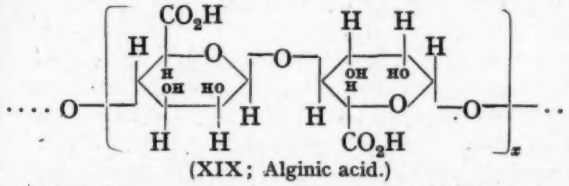


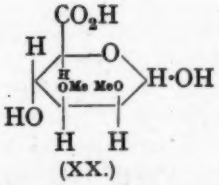
(XVIII; ε-Galactan.)

Gal = Galactopyranose residue, linked as shown. It is assumed that the trimethyl galactose residue is the 2 : 3 : 4-derivative.

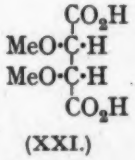
Another instance of a polyuronide is found in the alginic acid (XIX) obtainable from various types of seaweed. This consists solely of β-*d*-mannuronic acid residues in the pyranose form, linked through positions 1 and 4, since on methylation, followed by hydrolysis, it gives 2 : 3-dimethyl *d*-mannuronic acid (XX), which can be oxidised to inactive dimethoxysuccinic acid (XXI) with periodic acid and bromine water (Hirst, Jones, and Jones, J., 1939, 1880).



(XIX; Alginic acid.)



(XX.)



(XXI.)

Plant Gums.—A study of the plant gums which have been obtained from many species of *Rosaceæ* and *Leguminosæ* throws further light on the problems under discussion, since these substances form a series of structurally complex polysaccharides in which hexose residues, uronic acid residues, pentose residues, and methyl pentose residues occur combined with one another in the most diverse fashions within the same molecule. An opportunity is thus provided for comparative studies of the ring form and the mode of linkage of the various sugars. A review of present knowledge in this field reveals that arabinose is present in the furanose form and is attached as a side chain to the main chain of the molecule. On the other hand, xylose has been encountered so far only in the pyranose form. Galactose, which is usually in the main chain of the polysaccharide, also favours the pyranose form and is found usually in a 1 : 3- or 1 : 6-linkage rather than in the 1 : 4-linkage so characteristic of the glucose polysaccharides,

starch, cellulose, lichenin and glycogen. The uronic acid so far met with in the plant gums has been glycuronic acid, which is attached in the pyranose form to *d*-galactose or *d*-mannose. These generalisations have been arrived at from the study of several different gums, which, despite their diversity of type and structure, have certain points of resemblance. For instance, they all appear to possess a repeating unit comprised of an aldobionic acid residue united to two *d*-galactose residues, together with side chains of various types.

In determining the constitution of the gums it is essential that a homogeneous material be used. In the case of almond, cherry, damson, egg plum, lemon and orange gums the most satisfactory procedure is to collect the nodules of gum from one tree if possible, and examine selected nodules for homogeneity. Once it has been established that each type of tree produces a characteristic gum, its collection is much simplified. After purification of the gum, its equivalent weight, rotation, uronic anhydride and pentosan content are determined and from these figures the percentage content of pentosan present in the gum may be calculated. " Auto-hydrolysis " of the purified, ash-free gum results in removal of all the pentofuranose molecules from the polysaccharides, together with other sugars which may be attached to them,

TABLE II.

Approximate Composition of Plant Gums (mols. per repeating unit).

Gum.	*d*-Glycuronic acid or methoxy-deriv.	*d*-Galactose.	*d*-Mannose.	*l*-Arabinose.	*d*-Xylose.	*l*-Rhamnose.
Arabic	1	3	nil	2	nil	1
Damson	1	2	1	3	*ca.* 3%	nil
Cherry	1	2	1	6	*ca.* 3%	nil
Egg plum	2	6	nil	7	1	nil
Purple plum	1	3	nil	3(?)	1(?)	nil
Almond tree	1	3	nil	4	2	nil
Lemon	+ve	+ve	nil	+ve	nil	nil
Orange	+ve	+ve	nil	+ve	nil	nil
Grape fruit	+ve	+ve	nil	+ve	nil	nil
Cholla	+ve	+ve	nil	+ve	nil	+ve
Mesquite	*d*-Galacturonic	+ve	nil	+ve	nil	—

For references see text, except for cholla gum (Sands and Klaas, *J. Amer. Chem. Soc.*, 1929, **51**, 3441) and mesquite gum (Anderson and Sands, *Ind. Eng. Chem.*, 1925, **17**, 1257; *J. Amer. Chem. Soc.*, 1926, **48**, 3172).

and leaves the skeleton of the gum, which may still contain some pentose molecules united in the pyranose form. Further hydrolysis of this degraded polysaccharide results in the formation of an aldobionic acid, which usually consists of *d*-glycuronic acid united to another hexose, together with *d*-galactose and small quantities of other sugars. By this means some idea of the constituents of the gum, together with their order of linkage, is obtained. Further evidence on the mode and position of linkage is obtained from a study of the products of hydrolysis of the methylated aldobionic acid, degraded gum and original gum.

The plant gum which has been most extensively studied is gum arabic. This has been the subject of a series of detailed investigations by Dr. F. Smith of Birmingham University, and notwithstanding the difficult and complicated nature of the problem, so much progress has been made that the main features of the structure of the repeating unit have been elucidated and the possibilities remaining in structural detail have been very considerably narrowed down.

The nature of the constituent sugars of gum arabic had already been investigated, but some doubt remained as to the presence of *l*-rhamnose (Norman, *Biochem. J.*, 1929, **23**, 524). However, by autohydrolysis of the acidic polysaccharide, Smith demonstrated the presence of *l*-arabinose, *l*-rhamnose, and *d*-galactose. A portion of the galactose was isolated after partial hydrolysis of the gum in the form of a disaccharide, 3-*d*-galactosido-*l*-arabinose, the constitution of which was proved by the usual methods (Smith, J., 1939, 744). The constitution of the aldobionic acid which resulted from further hydrolysis of the degraded polysaccharide had already been determined as 6-*d*-glycuronosido-*d*-galactose (Challinor, Haworth, and Hirst, J., 1931, 258; Hotchkiss and Goebel, *J. Amer. Chem. Soc.*, 1936, **58**, 858). Prolonged autohydrolysis of the degraded gum gave small quantities of a disaccharide, 3-*d*-galactosido-*d*-galactose, the constitution of which was proved by hydrolysis of the completely methylated material and identification of the resulting sugars (Smith, J., 1940, 79). The isolation of these products is in itself sufficient demonstration of the complexity of the gum arabic molecule. Degraded arabic acid (obtained by autohydrolysis of the gum and consisting of nine residues of *d*-galactose and three residues of *d*-glycuronic acid) was then methylated. From an examination of the sugars resulting from hydrolysis of the methyl derivative (Smith, J., 1939, 1724), the presence of four end groups, one of *d*-galactopyranose and three of *d*-glycuronopyranose, was demonstrated. The hydrolysis products included also 2 : 3 : 4-trimethyl *d*-galactose (XV) (5 molecular proportions) and 2 : 4-dimethyl *d*-galactose (XIV) (3 molecular

proportions). The isolation of these proved that all the galactose molecules were in the pyranose form, all the linkages in the molecule were either 1 : 3 or 1 : 6, and the 1 : 4-linkage characteristic of starch

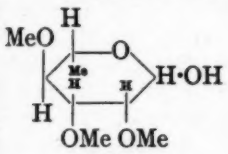
Gal 1, 3 Gal 1, 3 Gal 1, 3 Gal 1, 3 Gal 1, 3 Gal.....
Gal Gal Gal
Gly Gly Gly

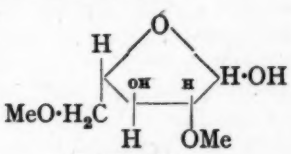
Degraded gum arabic.

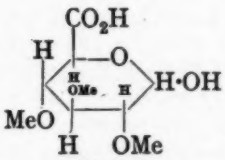
(Gal = *d*-galactopyranose; Gly = *d*-glycuronic acid, pyranose form)

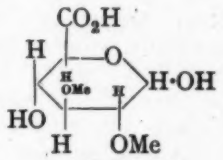
and cellulose was entirely absent. From these facts it was concluded that degraded gum arabic must have one of three formulæ. The possibilities for the structure of degraded gum arabic were further limited to two, by the isolation under carefully controlled conditions of hydrolysis of a hexamethyl 6-β-glucuronosido-*d*-galactose from methylated degraded arabic acid (Jackson and Smith, J., 1940, 74). One of these which illustrates the general type of structure is shown above.

From a study of the products of hydrolysis of methylated arabic acid, Smith was able to draw further conclusions as to the positions of the arabinose, rhamnose, and galactose units. Hydrolysis gave 2 : 3 : 4-trimethyl *l*-rhamnopyranose (XXII), 2 : 3 : 5-trimethyl (IV) and 2 : 5-dimethyl *l*-arabofuranose (XXIII), 2 : 3 : 4 : 6-tetramethyl (IX) and 2 : 4-dimethyl *d*-galactopyranose (XV) and 2 : 3 : 4-trimethyl (XXIV) and 2 : 3-dimethyl *d*-glucuronic acid (XXV).


(XXII.)


(XXIII.)


(XXIV.)


(XXV.)

"The identification of these products demonstrates the branched chain structure of arabic acid and also shows that those labile sugar residues, namely, *l*-arabinose, *l*-rhamnose, and 3-galactopyranosido-*l*-arabinose, which are liberated during the autohydrolysis of arabic acid, are joined to the nucleus of degraded arabic acid in the form of *l*-arabofuranose, *l*-rhamnopyranose, and 3-galactosido-*l*-arabofuranose" (Smith, J., 1940, 1035). In addition to the 1 : 3- and 1 : 6-linkages present in arabic acid, the 1 : 4-linkage also is present, since 2 : 3-dimethyl methyl-*d*-glucuronoside is one of the products isolated. Many formulæ, varying, however, only in detail, are ascribable to the undegraded gum arabic (one of which is shown below) on the above evidence, and still further work is required for the allocation of a definite detailed structure.

A 3, 1 Gal A 3, 1 Gal
Gal 1, 3 Gal 1, 3 Gal 1, 3 Gal 1, 3 Gal 1, 3 Gal.....
R 1, 3 Gal R 1, 3 Gal R 1, 3 Gal
Gly Gly Gly
A A A

Gal = *d*-Galactopyranose
Gly = *d*-Glycuronic acid
R = *l*-Rhamnopyranose
A = *l*-Arabofuranose

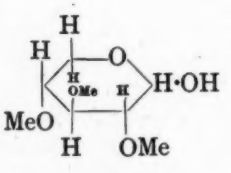
Gum arabic.

Structural investigations on damson gum have been carried out in the Bristol University laboratories. Samples of the gum were collected from trees in many different parts of the country and were found to be essentially the same in physical and chemical properties. The ash-free polysaccharide (A) had an equivalent weight of 1100, and estimation of pentosan and uronic anhydride indicated the presence of some 37·6% of araban and 16·4% of uronic anhydride. Autohydrolysis of the polysaccharide gave reducing sugars and a degraded polysaccharide. The sugars were shown to consist almost entirely of *l*-arabinose contaminated with a small quantity of *d*-galactose and the whole of the *l*-arabinose was removed from the polysaccharide during autohydrolysis. The degraded polysaccharide (B) obtained by autohydrolysis gave values for uronic acid and pentosan which were in agreement with those required by a polysaccharide containing one uronic acid residue, combined with three hexose residues, together with a pentosan present in much smaller stoicheiometric ratio. Controlled hydrolysis of this degraded polysaccharide with N-sulphuric acid gave two molecular proportions of *d*-galactose admixed with a little

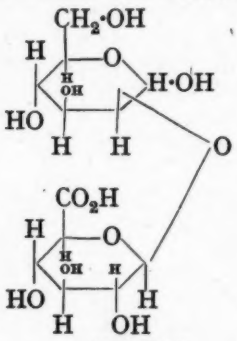
d-xylose and one molecular proportion of an aldobionic acid (2-*d*-glycuronosido-*d*-mannose). The aldobionic acid on further hydrolysis gave equimolecular proportions of *d*-mannose and *d*-glycuronic acid; the gum, therefore, consists of repeating units which contain the following sugars: *l*-arabinose (3 mols.), *d*-galactose (2 mols.), *d*-mannose (1 mol.), *d*-glycuronic acid (1 mol.). In addition, *d*-xylose occurs to the extent of about 3% (Hirst and Jones, J., 1938, 1174).

Further evidence on the structure of the gum was obtained from a study of the products of hydrolysis of the methylated gum (A) and of the methylated degraded gum (B). Methylation was carried out by heating the thallium derivative with methyl iodide—the product was essentially homogeneous and in each case was hydrolysed with methyl-alcoholic hydrogen chloride. The hydrolysed products from methylated damson gum (A) consisted of a complex mixture of methylated sugars, in which the following sugars were identified in the approximate molecular proportions indicated: 2 : 3 : 5-trimethyl *l*-arabinose (IV) (8 parts), 2 : 3-dimethyl *l*-arabinose (V) (4 parts), 2 : 4 : 6-trimethyl *d*-galactose (XVII) (3 or 2 parts), 2 : 4-dimethyl *d*-galactose (XV) (3 or 4 parts), 2 : 3 : 4-trimethyl *d*-glycuronic acid (XXIV) (2 parts), 2 : 3-dimethyl *d*-glycuronic acid (XXV) (2 parts), and a partially methylated *d*-mannose (4 parts). 2-Methyl galactose (1 part) and 4-methyl *d*-galactose (1 part) were also identified, but these may have been isolated as a result of incomplete methylation of the polysaccharide. A methylated derivative of *d*-xylose was also present, but was not identified (Hirst and Jones, unpublished results).

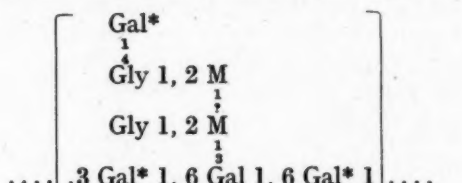
Methylated degraded gum (B) on hydrolysis gave the following sugar derivatives in approximately the molecular proportions indicated (Hirst and Jones, J., 1939, 1482): 2 : 3 : 4-trimethyl *d*-xylose (XXVI) (3—4%), 2 : 3 : 4 : 6-tetramethyl *d*-galactose (IX) (1 part), 2 : 3 : 4-trimethyl *d*-galactose (1 part), 2 : 4 : 6-trimethyl *d*-galactose (XVII) (1 part), 2 : 4-dimethyl *d*-galactose (XV) (1 part) (previously reported erroneously to be the 4 : 6-dimethyl derivative), 2 : 3 : 4-trimethyl *d*-glycuronic acid (XXIV) (1 part), and 2 : 3-dimethyl *d*-glycuronic acid (XXV) (1 part). A portion, at least, of the mannose (2 parts) is known to be a dimethyl derivative. The fully methylated undegraded damson gum gives neither tetramethyl nor 2 : 3 : 4-trimethyl galactose on hydrolysis, from which it may be inferred that the arabinose side chains are attached to positions C_6 and C_3 in those galactose residues which give rise to the above-mentioned sugars in the methylated degraded gum. Since 2 : 3-dimethyl and 2 : 3 : 5-trimethyl arabinose are present in the hydrolysis products in the ratio 1 : 2, it follows that the side chains in question have the structures A 1, 5 A 1 . . . and A 1 . . . respectively, where A = an arabofuranose residue. From these facts and from the observation that the aldobionic acid in damson gum consists of 2-*d*-glycuronosido-*d*-mannose (XXVII) some idea can be



(XXVI.)



(XXVII.)



(XXVIII; Degraded damson gum.)

Gal = Galactopyranose
Gly = Glycuronic acid (pyranose)
M = Mannopyranose

obtained of the type of structure present in the damson gum molecule. Neglecting, for the moment, the small proportion of xylose, the rôle of which is unknown, one of many possible structures for degraded damson gum is depicted in (XXVIII). In the undegraded gum the arabinose side chains may be attached to any of the galactose residues marked with an asterisk (at least two being involved). It is obvious that at this stage of the investigation, when detailed information concerning the mannose and xylose residues is lacking, it is not possible to indicate more than an outline of the type of structure involved.

Cherry gum (C) closely resembles damson gum in its physical properties but differs from it considerably in its chemical constitution. Its equivalent weight is very much higher (1503) and it contains more pentosan (Butler and Cretcher, *J. Amer. Chem. Soc.*, 1931, **53**, 4160; Jones, J., 1939, 558). Analysis indicates that it contains the following sugars in the approximate proportions indicated: *l*-arabinose (6 parts), *d*-xylose (*ca.* 1·5%), *d*-galactose (2 parts), *d*-mannose (1 part), and *d*-glycuronic acid (1 part). Autohydrolysis of the acidic gum (C) results in the removal of practically all the pentose, together with a little *d*-xylose, leaving a degraded cherry gum (D) which very closely resembles the degraded gum from

the damson. On further hydrolysis this gives two molecular proportions of *d*-galactose together with an aldobionic acid, 1 : 2-*d*-glycuronosido-*d*-mannose, identical with the aldobionic acid present in damson gum. Both cherry gum (C) and degraded cherry gum (D) are readily methylated by thallium hydroxide and methyl iodide.

Methylated cherry gum (C) gives on hydrolysis (Jones, unpublished results) a complex mixture of sugars, among which the following have been identified: 2 : 3 : 5-trimethyl *l*-arabinose (IV), 2 : 5-dimethyl *l*-arabofuranose (XXIII), 2 : 4 : 6-trimethyl *d*-galactose (XVII), 2 : 4-dimethyl *d*-galactose (XV), 2 : 3 : 4-trimethyl *d*-glycuronic acid (XXIV), and a dimethyl *d*-glycuronic acid (2·3?). A derivative or derivatives of *d*-mannose and *d*-xylose remain to be identified. It is possible that degraded cherry gum (the polysaccharide obtained by autohydrolysis of the original gum) has the same general structure as is present in degraded damson gum, but these investigations were interrupted by the outbreak of war.

Our state of knowledge of other plant gums is not so advanced, but some information (Hirst and Jones, unpublished) has been obtained concerning egg plum, purple plum, almond, grape-fruit, orange and lemon tree gums (for composition, see Anderson, Russell, and Seigle, *J. Biol. Chem.*, **1936**, **113**, 683).* For example, egg plum gum is an acidic polysaccharide which consists of residues of *l*-arabinose (7), *d*-xylose (1), *d*-galactose (6), and *d*-glycuronic acid (2) in approximately the proportions indicated. All the arabinose units appear to be in the furanose form, since they are eliminated under very mild conditions of hydrolysis. The *d*-xylose appears to be united in the pyranose form to a molecule of *l*-arabinose and the *d*-galactopyranose units are united to an aldobionic acid (*d*-glycuronosido-*d*-galactose) (1 : 6?).

Almond tree gum on autohydrolysis gives *l*-arabinose and a disaccharide which on further hydrolysis gives *d*-xylose and *l*-arabinose. The degraded gum remaining after removal of the pentose gave on further hydrolysis *d*-galactose and an aldobionic acid, 1-glycuronosido-6-*d*-galactose, identical with the aldobionic acid in gum arabic. Almond tree gum, therefore, contains the following sugar residues: *l*-arabinose (4 parts), *d*-xylose (2 parts), *d*-galactose (2 parts), aldobionic acid (1 part).

Mucilages.—Of the mucilages examined, those from slippery elm (Anderson, *J. Biol. Chem.*, 1934, **104**, 163), flax seed (*idem*, *ibid.*, 1933, **100**, 249), lucerne seed (May and Schulze, *Z. Biol.*, 1936, **97**, 201), *plantago lanceolata* seed (Mullan and Percival, J., 1940, 1501), *plantago psyllium* seed (Anderson and Fireman, *J. Biol. Chem.*, 1935, **109**, 437), and *plantago fastigiata* seed (Anderson, Gillette, and Seeley, *ibid.*, 1941, **140**, 569) may be referred to briefly.

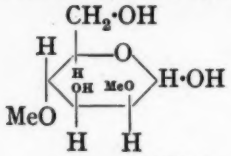
It appears that all these mucilages may contain a protein-like compound as an integral part of the molecule. The mucilages from the seeds of *plantago psyllium* and of *plantago fastigiata* have both been shown to contain *l*-arabinose, *d*-xylose, and *d*-galacturonic acid. *Plantago fastigiata* mucilage contains an aldobionic acid consisting of *d*-galacturonic acid and *l*-arabinose, but knowledge of the detailed constitution of this aldobionic acid is not yet available. On the evidence presented it is just possible that the *l*-arabinose molecules may occur in the mucilage in the pyranose form, as they seem to be more resistant to hydrolysis, but further work is needed to settle this point. The mucilage from *plantago lanceolata* resembles those from *plantago psyllium* and *plantago fastigiata* in that it contains *d*-galacturonic acid and *d*-xylose, but differs in that it also contains *d*-galactose and a methyl pentosan, but no *l*-arabinose. Its structure appears to comprise many side chains of *d*-xylose. Very little is known of the detailed structural constitution of flax seed mucilage and only the aldobionic acid obtainable from it has been critically examined (Tipson, Christman, and Levene, *J. Biol. Chem.*, 1939, **138**, 609).

On the other hand, some evidence concerning the ring structure and linkage of the component sugars of lucerne seed mucilage and of slippery elm mucilage has been obtained. Lucerne seed mucilage gives on hydrolysis two sugars only, namely, *d*-galactose (2 parts) and *d*-mannose (1 part) (compare May and Schulze, *loc. cit.*). Attempts to separate the polysaccharide into a galactan and a mannan were fruitless and a study of the products of hydrolysis of the methylated product showed that the two sugars are combined together in the same polysaccharide.

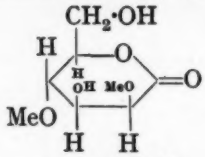
The purified lucerne seed mucilage was a cream powder soluble in water, giving viscous solutions, and it underwent slow hydrolysis with N-sulphuric acid, the presence of pyranose rings being thus indicated (compare the mannogalactan of the seeds of the fenugreek; Daoud, *Biochem. J.*, 1932, **26**, 255). The methylated product, which was free from protein, gave on hydrolysis three methylated sugar derivatives in approximately equal proportions (Hirst, Jones, and Walder, unpublished results); these were 2 : 3 : 4 : 6-tetramethyl *d*-galactose (IX), 2 : 4 : 6-trimethyl *d*-galactose (XVII), and a mannose derivative which was almost certainly 3 : 4-dimethyl *d*-mannose (XXIX), since it gave no furanose derivative with cold methyl-alcoholic hydrogen chloride and on oxidation gave a δ-lactone (XXX) which with liquid ammonia

* We are indebted to Dr. Misener of Toronto for the gift of orange, lemon, and grapefruit gums.

gave an amide with a positive Weerman reaction. From these results, taken in conjunction with the rotation of the polysaccharide (+ 85°), one of the possible formulæ is outlined below (XXXI).



(XXIX.)



(XXX.)

Gal Gal Gal
1 1 1
3 3 3
.....6 M 1, 3 Gal 1, 6 M 1, 3 Gal 1, 6 M 1, 3 Gal.....

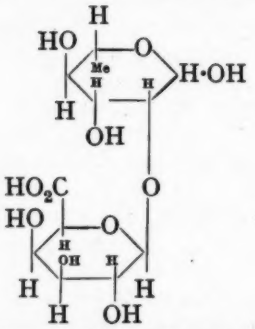
(XXXI; Lucerne seed mucilage.)

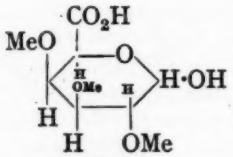
(Gal = galactopyranose; M = mannopyranose)

Slippery elm mucilage, in addition to some 10% of protein, contains *d*-galacturonic acid (1 part), *l*-rhamnose (1 part), and *d*-galactose (1 part). The ash-free mucilage, on being heated, is partly hydrolysed with the precipitation of coagulated protein; the protein-free polysaccharide underwent further hydrolysis at a rate normal for a pyranoside and gave rise to *d*-galactose and an aldobionic acid. The latter was *d*-galacturonosido-*l*-rhamnose, since on further hydrolysis it gave *d*-galacturonic acid and *l*-rhamnose (Anderson, *loc. cit.*).

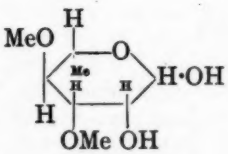
Complete methylation of the aldobionic acid, followed by hydrolysis of the products, proved its structure (Gill, Hirst, and Jones, J., 1939, 1469) (XXXII) to be identical with that of the aldobionic acid present in flax seed mucilage (Tipson, Christman. and Levene, *loc. cit.*), since it gave equimolecular proportions of 2 : 3 : 4-trimethyl *d*-galacturonic acid (XXXIII) and 3 : 4-dimethyl *l*-rhamnose (XXXIV). The linkage is evidently between the reducing group of the galacturonic acid and C_2 of the rhamnose molecule—an unusual type found hitherto only in aldobionic acids in damson and cherry gums and flax seed mucilage.

(XXXII.)





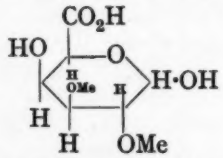
(XXXIII.)

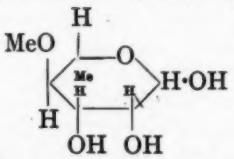


(XXXIV.)

Methylation of the mucilage with sodium hydroxide and methyl sulphate proceeded unsatisfactorily; methylation by means of thallous hydroxide and methyl iodide, however, proceeded smoothly and rapidly. The methylated polysaccharide was comparatively stable to methyl-alcoholic hydrogen chloride and prolonged boiling with this reagent was necessary for completion of hydrolysis. Fractionation of the

(XXXV.)





(XXXVI.)

Galac 1, 2 R 1, 4 Galac 1, 2 R 1, 4 Galac 1, 2 R 1, 4 Galac 1, 2, R1,.....

Gal Gal
3 3
1 1
Gal Gal
4
1
Gal

(XXXVII; Slippery gum mucilage.)

Gal = *d*-Galactopyranose R = *l*-Rhamnopyranose Galac = *d*-Galacturonic acid (pyranose)

products gave 2 : 3 : 4-trimethyl *d*-galacturonic acid (trace) (XXXIII), 2 : 3-dimethyl *d*-galacturonic acid (4 parts) (XXXV), 2 : 3 : 4 : 6-tetramethyl *d*-galactose (2 parts) (IX), 2 : 4 : 6-trimethyl *d*-galactose (1 part) (XVII), 2 : 3 : 6-trimethyl *d*-galactose (1 part) (VIII), 3 : 4-dimethyl *l*-rhamnose (2 parts) (XXXIV), and 4-methyl *l*-rhamnose (2 parts) (XXXVI). From the evidence given, the general type of structure present in the mucilage may be inferred and one formula which illustrates typical features is (XXXVII) (Gill, Hirst, and Jones, unpublished results). There are obvious variants, but other methods of approach must be developed before it will be possible to differentiate unequivocally between them.

Some Aspects of Algal Chemistry.

EIGHTH HUGO MÜLLER LECTURE DELIVERED ON OCTOBER 16TH, 1941.

By I. M. HEILBRON, D.S.O., D.Sc., F.R.S.

TWENTY years have passed since a Hugo Müller lecture has been directed to a botanical subject. On that occasion, the late Professor Benjamin Moore dealt with the fundamental problem of photosynthesis (J., 1921, **119**, 1555). It must be admitted that from the angle of organic chemistry our knowledge of this all-important chemical process has not advanced appreciably during the intervening years. In many other directions, however, the past twenty years have proved astonishingly fruitful in adding to our knowledge concerning the diverse materials elaborated by the living plant. Thus we have witnessed on the one hand the unravelling of the structures of the sugars, starches, and cellulose, those all-important primary products of photosynthesis. Further, the essential structure of chlorophyll has been elucidated and its total synthesis will doubtless be achieved within the next decade. Again, other pigments common to the Higher Plants, the anthocyanins and carotenoids have also been fully examined and their constitutions determined. A whole host of other biologically active substances of most varied character, hormones, vitamins, and enzymes, have been isolated and in many cases synthesised, and the detailed study of their reactions has led to a fuller understanding of biological processes.

It is curious that in this galaxy of discovery the study of the Algæ has, from the chemical aspect, largely remained in a side-channel, the more so as among members of this branch of the Thallophyta are to be found many of the simplest types of unicellular forms which one would reasonably expect to provide ideal material for the investigation of the still obscure life processes of the living cell, notably

TABLE I.

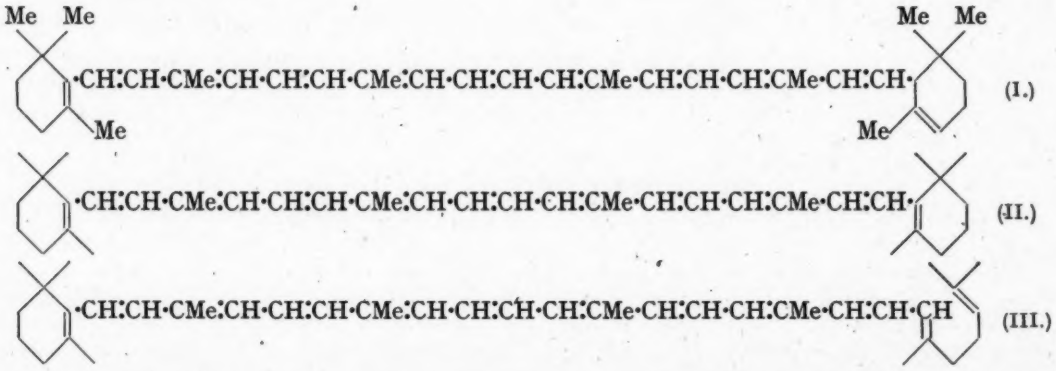
Algæ.

Class.	Pigments.	Food reserve.	Cell wall.	Structure.	Reproductive cells.	Habitat.	No. of Species.
Chlorophyceæ	Grass-green algæ. Plastids contain same pigments, in same proportion, as Higher Plants	Usually starch	Mainly cellulose	Unicellular or filamentous or multicellular	Motile cells with equal flagellæ. Sexual and asexual reproduction	Freshwater with marked terrestrial tendency. Few marine	5700
Xanthophyceæ	Yellow-green plastids. Similar pigments to Chlorophyceæ, but with excess of carotene	Usually oil or leucosin	Rich in pectin compounds and silica	Unicellular or simple filaments	Motile reproductive cells with flagellæ unequal in length	Mainly freshwater	150
Chrysophyceæ	Yellow-golden brown plastids	Fats and leucosin	Pectin, cellulose, sometimes silica	Unicellular or colonial	Motile cells with one or two cilia. Sexual reproduction not known	Mostly freshwater. Particularly plankton in lakes	210
Bacillariophyceæ (Diatoms)	Yellow or brown plastids	Fats and volution, never starch	Pectin substance, impregnated with silica	Unicellular	No ciliated cells	Freshwater and marine	5300
Cryptophyceæ	Brownish plastids	Starch or starch-like compound	Mostly naked protoplast	Unicellular	Motile cells. Two unequal flagellæ	Mostly freshwater. Few marine	30
Dinophyceæ	Golden to chocolate-brown plastids (few species without plastids)	Starch or oil	Elaborated cellulose plates	Mostly unicellular	Motile cells with cilia. Sex reproduction rare	Mostly marine	960
Chloromonadineæ	Bright green plastids with excess of xanthophyll	Oil		Unicellular	Motile cells with two almost equal cilia	Freshwater only	*ca.* 6
Euglenineæ	Grass-green or colourless plastids	Paramylon (related to starch) or fats	No cell wall, *i.e.*, naked protoplast	Unicellular	Motile cells with one, two or three flagellæ. Sexual reproduction very rare	Almost all freshwater	335
Phæophyceæ	Normal pigments masked by golden-brown fucoxanthin; proportion of chlorophyll *b* less than in Chlorophyceæ	Stored in dissolved state like sugar-storing Higher Plants	Inner of cellulose, outer of pectin compound	Always multicellular. Largest and most complex Algæ	Motile cells with two lateral cilia. Sexual reproduction normal	Almost exclusively marine and generally of colder waters	900
Rhodophyceæ	Pigments contain red, water-soluble phycoerythrin in addition to usual pigments. Sometimes blue phycocyanin as well, especially under intense illumination	Insoluble floridean starch. Some contain a galactoside of glycerol as well	Cellulose and pectin compounds	Mostly multicellular, somewhat complex plant body	No motile cells at all. Sexual reproduction of specialised kind	Mostly marine. A few species in freshwater	2500
Myxophyceæ	Unlike all other algæ, pigments *not* in plastids but diffuse through outer layers of protoplasm. Blue-green colour due to addition of blue phycocyanin, sometimes red phycoerythrin as well	Sugars and glycogen	Mainly cellulose. Pectin outer. Mucilage coat	Unicellular or filamentous	No motile reproductive cells. No sexual reproduction	Mainly freshwater	1400

photosynthesis and reproduction. To some extent, this lack of interest may be due to the difficulty of obtaining the required material, but it seems to me that a more likely explanation is the lack of sufficiently close collaboration in this country between the various branches of Science. In directing attention to-day to the Algæ, I intend to confine my remarks to the lipoid constituents with special reference to the carotenoids and sterols. According to the eminent algologist Fritsch, the Algæ are most suitably divided into eleven distinct Classes (Fritsch, " Structure and Reproduction of the Algæ," Cambridge University Press, 1935). This classification is based very largely upon the colour of the pigments contained in the chromatophores, but other factors, such as reserve foods, form and propagative methods, are also taken into account. A summary of the main characteristics of each Class is reproduced in Table I, from which it will be noted that the colour factor is indeterminate, a fact borne out by a literature search, which reveals an almost complete lack of precise information concerning the individual pigments of the various Classes (compare also Boresh, " Handbuch der Pflanzenanalyse," Vienna, 1932). The first methodical attempt to clarify the position was made by Kylin (*Z. physiol. Chem.*, **1927**, **166**, 39), who, using a capillary method of analysis, identified by means of absorption bands ten carotenoids in various types of Algæ. As, however, Kylin's work was purely of a qualitative nature, and as many of the pigments named by him have no parallel in modern carotenoid nomenclature, it seemed desirable to undertake a fresh and comprehensive study of the subject, examining representatives of each Class, including as far as possible Algæ of the various Orders.* Our aims were, first, to relate the algal pigments, so far as possible, to those of the Higher Plants, or failing such relationship, to elucidate their chemical constitution. We hoped further to establish by this chemical analysis the validity or otherwise of the accepted botanical relationship between colour and classification and finally we considered it likely that this study would throw light upon other biological and physiological factors. Although it has as yet been impossible to cover the whole field, we have been successful in examining Algæ selected from seven of the eleven Classes into which Fritsch has classified them. Moreover, during the course of our work details of investigations carried out in certain Continental laboratories have appeared with the result that our knowledge concerning the carotenoid pigments of the Algæ is now almost as extensive as that of the Phanerogams.

As already mentioned, we have included an examination of the sterols in our survey, and many interesting points have emerged from this study which, we believe, may not be without significance in relation to sexual reproduction.

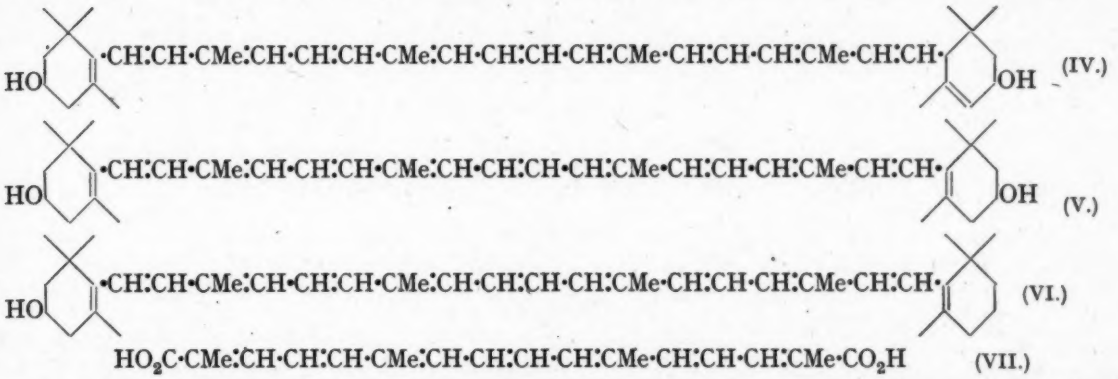
Before dealing with the individual lipoid pigments found in the Algæ, I would like to recall to you the structures of certain characteristic carotenoids of the Higher Plants. Here, first and foremost, stand carotene and " xanthophyll," which pigments invariably occur associated with chlorophylls *a* and *b* in all green leaves (Willstätter and Stoll, " Untersuchungen über die Assimilation der Kohlensaure," Berlin, 1913), and are therefore the most widely distributed, naturally occurring organic compounds. As is well known, at least three isomeric carotenes (α, β and γ) occur in Nature, the structures of which are shown in the formulæ (I), (II), and (III).



Similarly, leaf xanthophyll is a complex mixture of isomers (Kuhn, Winterstein, and Lederer, *Z. physiol. Chem.*, **1931**, **197**, 141), of which lutein (IV) is the main constituent, but according to Strain (" Leaf Xanthophylls," Carn. Inst. Wash., Pub. No. **490**, 1938) the isomeric zeaxanthin (V) is also

* I desire to take this opportunity of placing on record the indebtedness of my chemical collaborators and myself to Mr. P. W. Carter of the Botany Department, University College of Wales, Aberystwyth, for his enthusiastic co-operation, not only in the difficult task of collecting the various classes of pure Algæ, but more especially in connexion with the correlation of chemical factors with botanical classification.

invariably present in small amount, as are also kryptoxanthin (VI) and the structurally indefinite pigments flavoxanthin, $C_{40}H_{56}O_3$, and violaxanthin, $C_{40}H_{56}O_4$. The only other carotenoids of the Higher Plants of which mention need be made are crocin and crocetin (VII), the former of which is the digentiobiose ester of the latter (Karrer and Kiki, *Helv. Chim. Acta*, 1929, **12**, 985). Crocetin itself is capable of existence in *cis*- and *trans*-forms and the corresponding dimethyl esters have been isolated and found to differ appreciably in their light absorption, the labile *cis*-isomer having its absorption maxima displaced



towards the ultra-violet (Kuhn and Winterstein, *Ber.*, 1933, **66**, 209). I do not propose to discuss the methods of extraction and isolation of the individual algal pigments, as these have already been described in detail elsewhere (Carter, Heilbron, and Lythgoe, *Proc. Roy. Soc.*, 1939, *B*, **128**, 62; see also Kylin, *K. fysiogr. Sällsk. Lund. Forh.*, 1939, **9**, 1). Whenever possible we have attempted to isolate the pigments and characterise them by melting point, crystalline form, absorption maxima and specific colour reactions. Reliance solely upon spectroscopic or adsorption evidence can well be misleading, as the carotenoids readily undergo spontaneous isomerisation (Zechmeister and Tuzson, *Biochem. J.*, 1938, **32**, 1305; *Ber.*, 1939, **72**, 1340), giving labile isomerides which may spectroscopically simulate some other pigment. Thus β-carotene isomerises readily into ψ-α-carotene, which has absorption maxima identical with those of α-carotene (Carter and Gillam, *Biochem. J.*, 1939, **33**, 1320).

Among the Algæ the Chlorophyceæ or Green Algæ comprise a very large number of diverse forms, many of which are freshwater, while others are terrestrial or marine. The first detailed examination of any member of this group was made by Willstätter and Page (*Annalen*, 1914, **404**, 237), who, working with *Ulva lactuca*, a marine green alga growing between tide marks, observed carotene and xanthophyll. We have now examined nine individuals of the Chlorophyceæ and, as shown in Table II, in every case these pigments have been observed. *Trentepohlia aurea*, a strictly terrestrial alga, requires special mention. It occurs attached to rocks, tree trunks, and generally in regions of rather high rainfall as an orange-yellow felt, the colour of which was attributed by Cohn to the presence of a special orange-red pigment which he named hæmatochrome (*Arch. microsk. Anat.*, 1867, **3**, 44). We have now found that the actual pigment is β-carotene, the content of which in this alga is unusually high, being of the order of 0·2% of the dry weight. As in dry leaves of land plants the percentage of carotene averages 0·05%, it will be seen that *Trentepohlia aurea* is one of the richest sources of carotene hitherto described (compare also Tischer, *Z. physiol. Chem.*, 1936, **243**, 103). On the other hand, xanthophyll is only present in minute amount, whereas in other Chlorophyceæ and also in the Higher Plants the xanthophyll–carotene ratio is of the order 2—5 : 1 (Willstätter and Page, *loc. cit.*; see also Seybold and Egle, *Jahrb. wiss. Bot.*, 1938, **86**, 50). Another interesting observation is that *Trentepohlia*, unlike other members of the Class, is deficient in sterol, and in this respect resembles members of the Myxophyceæ which will be referred to later.

We have not in all cases attempted a complete separation of the carotene isomers, but in general β-carotene very largely predominates, sometimes indeed to the complete exclusion of the α-isomeride. Similarly, under " xanthopyll " we mean here the mixed hypophasic pigment which is predominantly lutein. In many cases, in addition to the typical lutein absorption maxima at 5060, 4730, and 4410 A., other maxima at 5000 and 4720 A. have been observed which may be due either to *neo*lutein (Zechmeister and Tuzson, *loc. cit.*), or possibly to some closely related xanthophyll of the type Strain (*loc. cit.*) has observed in the xanthophyll of the Higher Plants. Kylin (1939, *loc. cit.*) claims that he has obtained spectroscopic evidence of the presence of Strain's violaxanthin *b* in the green algæ examined by him. This pigment corresponds to the phylloxanthin of his earlier publications (*Z. physiol. Chem.*, 1927, **166**, 39)

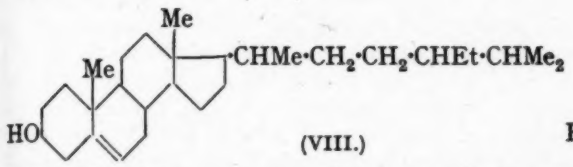
TABLE II.

Genus and species.	Order.	(1).	(2).	(3).	(4).	(5).	(6).	(7).	(8).	(9).	(10).	(11).	(12).
					Chlorophyceæ.								
Ulva lactuca	Ulotrichales	+	.	.	+	.	.	.	.	.	+	.	.
Enteromorpha compressa	,,	+	.	.	+	.	.	.	.	.	+	.	.
Cladophora Sauteri	Cladophorales	+	.	.	+	.	.	.	.	.	+	+	.
Trentepohlia aurea	Chætophorales	+	.	.	+	.	.	.	.	.	.	.	.
Pleurococcus Nægelii	,,	+	.	.	+	.	.	.	.	.	+	.	.
Œdogonium	Œdogoniales	+	.	.	+	.	.	.	.	.	+	.	.
Zygnema pectinatum	Conjugales	+	.	.	+	+	.	.	.	.	+	.	.
Vaucheria hamata	Siphonales	+	.	.	+	.	+	.	.	.	+	.	.
Nitella opaca	Charales	+	.	.	+	.	.	.	.	.	+	+	.
					Xanthophyceæ.								
Botrydium granulatum	Heterosiphonales	+	.	.	.	.	.	+	.	+	+	.	.
					Bacillariophyceæ.								
Nitzschia closterium	Pennales	+	.	.	+	+	.	.	.	.	.	+	+
					Chrysophyceæ.								
Apistonema Carteri	Chrysomonadales	+	.	.	+	+	.	.	.	.	.	+	+
Thallochrysis litoralis	,,												
Glœochrysis maritima	,,												
					Phæophyceæ.								
Pilayella littoralis	Ectocarpales	+	.	.	+	+	.	.	.	.	.	+	.
Ectocarpus tomentosus	,,	+	.	.	+	+	.	.	.	.	.	+	.
Sphacelaria cirrhosa	Sphacelariales	+	.	.	?	+	.	.	.	.	.	+	.
Stypocaulon scoparium	,,	+	.	.	?	+	.	.	.	.	.	+	.
Cladostephus spongiosus	,,	+	.	.	.	+	.	.	.	.	.	+	.
Dictyota dichotoma	Dictyotales	+	.	.	?	+	.	.	.	.	.	+	.
Chorda filum	Laminariales	+	.	.	.	+	.	.	.	.	.	+	.
Laminaria digitata	,,	+	.	.	.	+	.	.	.	.	.	+	.
Fucus ceranoides	Fucales	+	.	.	.	+	.	.	.	.	.	+	.
Fucus vesiculosus	,,	+	.	.	.	+	.	.	.	.	.	+	.
Ascophyllum nodosum	,,	+	.	.	.	+	.	.	.	.	.	+	.
Halidrys siliquosa	,,	+	.	.	.	+	.	.	.	.	.	+	.
					Rhodophyceæ.								
Porphyra umbilicalis	Bangiales	+	.	.	+	.	.	.	.	+	.	+	.
Lemanea mamillosa	Nemalionales	+	.	.	+	.	.	.	.	+	+	.	.
Gelidium corneum	Gelidiales	+	.	.	+	.	.	.	.	.	+	.	.
Dilsea edulis	Cryptonemiales	+	.	.	+	.	.	.	.	.	Too little material available for identification		
Polyides rotundus	,,	+	.	.	+	.	.	.	.	.			
Corallina officinalis	,,	+	.	.	+	.	.	.	.	.	.	.	+
Polysiphonia fastigiata	Ceramiales	+	.	.	+	.	.	.	.	.	+	.	.
Polysiphonia nigrescens	,,	+	.	.	+	+	.	.	.	.	.	+	.
Ceramium rubrum	,,	+	.	.	+	.	.	.	.	.	+	.	.
Chondrus crispus	Gigartinales	+	.	.	+	.	.	.	.	.	+	.	.
Gigartina stellata	,,	+	.	.	+	.	.	.	.	.	+	.	.
Phyllophora membranifolia	,,	+	.	.	+	.	.	.	.	.	+	.	.
Ahnfeltia plicata	,,	+	.	.	+	.	.	.	.	.	.	.	+
Rhodymenia palmata	Rhodymeniales	+	.	.	+	.	.	.	.	.	.	+	.
Plocamium coccineum	,,	+	.	.	+	.	.	.	.	.	+	.	.
					Myxophyceæ.								
Oscillatoria rubescens	Hormogonales	+	+	+	+	.	.	+	+	.	.	.	.
Rivularia atra	,,	+	+	+	+	.	.	.	.	.	.	.	.
Rivularia nitida	,,	+	+	+	+	.	.	.	.	.	.	.	.

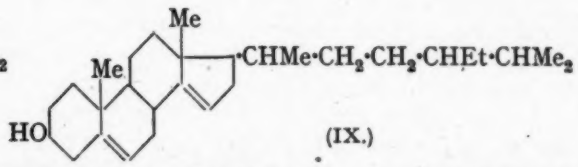
Column (1) Carotene; (2) Myxoxanthin; (3) Other epiphasic pigments; (4) Xanthophyll; (5) Fucoxanthin; (6) Violaxanthin; (7) Flavoxanthin; (8) Myxoxanthophyll; (9) Other hypophasic pigments; (10) Sitosterol; (11) Fucosterol; (12) Other sterols.

which he distinguishes from ordinary xanthophyll by the blue-green colour given with 25% hydrochloric acid. He also claims to find traces of zeaxanthin (previously named by him phyllorhodin). We ourselves have identified violaxanthin only in *Vaucheria hamata*, from which a crystalline specimen was obtained. This member of the Siphonales is known to be abnormal, being one of the few Chlorophyceæ which regularly store their food reserve as oil instead of starch, and the arrangement of its cilia is also unusual. It is intriguing to speculate on the cause of these divergencies and one wonders how far they find their origin in the unusual pigmentation of the chromatophore—is the pigment the directive influence or do the abnormal factors mentioned above determine the nature of the pigment? An examination of *Zygnema pectinatum*, a yellowish-green alga found in ponds and streams, has revealed the presence of fucoxanthin, which is the characteristic carotenoid of the Phæophyceæ. According to the botanists no abnormality in the life cycle or habitat of this alga is known, and here again the occurrence of an unusual xanthophyll can only be a matter for conjecture; is the chemical analysis revealing the phylogenetic past or is it pointing to some impending change? Apart from these abnormalities, this recent work strongly supports

the view held by most algologists, that the terrestrial plants originated among the more advanced members of the Chlorophyceæ. Our examination of the sterols present in members of this Class adds weight to the above view. It is known that the characteristic sterol of the Phanerogams is sitosterol (VIII) and we have observed its presence without exception in all the Chlorophyceæ examined by us, independent of habitat (Carter, Heilbron, and Lythgoe, *loc. cit.*). In the case of *Cladophora sauteri* and *Nitella opaca*, both members of somewhat specialised orders, the presence of fucosterol of probable structure (IX), the typical sterol of the Phæophyceæ, has also been observed (Heilbron, Parry, and Phipers, *Biochem. J.*, 1935, **29**, 1976).



(VIII.)



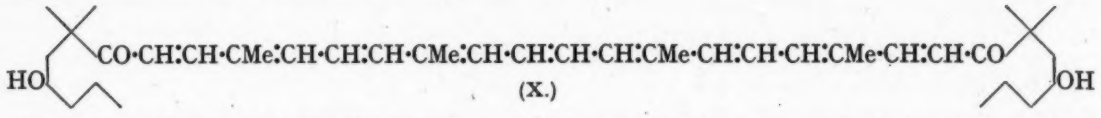
(IX.)

The Xanthophyceæ, named owing to their yellow-green chromatophores, form a small distinctive Class which at one time was included with the Chlorophyceæ. Unfortunately we have only been able to examine one member, the common mud-alga *Botrydium granulatum*. β-Carotene has been definitely identified and among the hypophasic lipochromes we have observed the presence of a pigment having well-defined absorption maxima at 4750 and 4470 A. and giving a strong blue colour with 25% hydrochloric acid. The absorption values are in exact agreement with those recorded by Kuhn and Brockmann (*Z. physiol. Chem.*, 1932, **213**, 192) for flavoxanthin. The only information in the literature concerning the xanthophyll of the Xanthophyceæ is the recognition that it gives a blue colour with concentrated hydrochloric acid. This could apply to either violaxanthin or flavoxanthin, but the spectrographic evidence excludes the former, and thus it may well be that flavoxanthin is characteristic of all the Xanthophyceæ.

Pascher has suggested (*Ber. deutsch. Bot. Ges.*, 1921, **39**, 236) a relationship, probably from a common ancestry, between the Xanthophyceæ, Bacillariophyceæ and Chrysophyceæ. His views are based on a number of similarities such as absence of starch, deposition of silica, and certain resemblances in the structure of the cellular envelopes. In order to ascertain whether this evidence of relationship extends to the carotenoids and sterols we have examined *Nitzschia closterium* as representing the Bacillariophyceæ (Diatoms) and also a mixture of three members of the Chrysophyceæ, *Apistonema Carteri Anand.*, *Thallochrysis litoralis Anand.*, and *Glœochrysis maritima Anand.*, kindly collected and classified for us by Professor Fritsch. From both Classes we have isolated identical carotenoids, *viz.*, carotene, lutein, and fucoxanthin; the analogy extends also to the sterols, where we find only fucosterol (see Table II). This analysis strongly supports Pascher's view that the Bacillariophyceæ and Chrysophyceæ have points of affinity and we suggest they are also possibly connected with the more primitive orders of the Phæophyceæ (Ectocarpales). On the other hand no affinity between these Classes and the Xanthophyceæ is observed, although admittedly the opportunity of drawing conclusions has been restricted by paucity of material.

Reference has already been made to the Phæophyceæ or Brown Algæ, a Class possessing botanical features of quite distinctive character. In appearance they vary in colour from olive-green to dark brownish-black and many varieties are among the largest of marine flora. The typical chromolipoid is fucoxanthin, which was first isolated and analysed by Willstätter and Page (*loc. cit.*) and given the formula $C_{40}H_{56}O_6$ or $C_{40}H_{54}O_6$. The pigment has absorption maxima at 5100, 4770, and 4450 A. and in this respect resembles α-carotene and lutein. It is further characterised by the deep blue colour it gives with hydrochloric acid and more especially by its extreme lability towards alcoholic alkali, which converts it into *iso*fucoxanthin (Heilbron and Phipers, *Biochem. J.*, 1935, **29**, 1369), which is more basic in character than the natural pigment as shown by the fact that it gives a blue colour with even dilute acetic acid. In *iso*fucoxanthin the absorption maxima are displaced towards the ultra-violet with the band heads at 4740 and 4480 A., similar to flavoxanthin. This susceptibility to alkali sharply differentiates fucoxanthin from violaxanthin and flavoxanthin. The structure of fucoxanthin is still obscure, but its ease of conversion into *iso*fucoxanthin recalls the similar conversion of astaxanthin into astacene (*q.v.*). Of its six oxygen atoms, four are present as hydroxyl groups (Heilbron and Phipers, *loc. cit.*) and catalytic hydrogenation (Karrer, Helfenstein, Wehrli, Pieper, and Morf, *Helv. Chim. Acta*, 1931, **14**, 614) discloses the presence of ten double bonds, all of which, judging by the absorption data, must be conjugated. All attempts to demonstrate the presence of carbonyl groups have proved abortive, but this does not necessarily exclude their presence, as capsorubin (X) also fails to form any ketonic derivatives (Zechmeister and

v. Cholnoky, *Annalen*, 1935, **516**, 30). Apart from fucoxanthin, Willstätter and Page (*loc. cit.*) record the presence of both carotene and xanthophyll in the Phæophyceæ, although the latter pigment was only assessed colorimetrically and never actually isolated.



(X.)

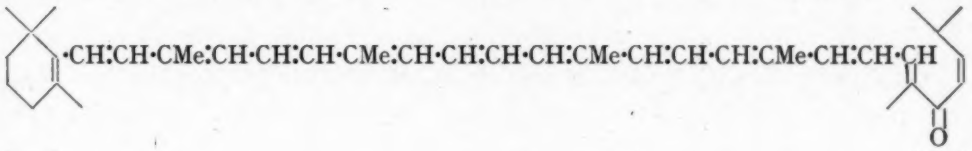
In our investigations of the Phæophyceæ we have extended the survey to include members from various Orders of these brown algæ and find that, despite the great diversity in the life cycles of the individual species, all reveal the most marked uniformity of pigmentation with fucoxanthin largely replacing lutein as the main hypophasic pigment. Indeed, as shown in Table II, we were only able to demonstrate the presence of the latter spectroscopically in the lower members of the Class and not in the more massive plants. A curious phenomenon has been noted in the case of dry *Fucus vesiculosus*; here fucoxanthin is absent but zeaxanthin makes its appearance and Heilbron and Phipers (*loc. cit.*) suggest that this pigment is a *post mortem* product of the fucoxanthin. This view is not shared by Kylin (1939, *loc. cit.*), who claims to find by spectroscopic and chromatographic methods xanthophyll (lutein?), zeaxanthin and violaxanthin *b* in small amounts in fresh *Ectocarpus siliculosus* and *Fucus vesiculosus*. He suggests that as the alga dries, the fucoxanthin is rapidly destroyed (see Willstätter and Page, *loc. cit.*) and that the zeaxanthin already present, being more resistant to oxidation than the other xanthophylls, is naturally observed with ease in the dry material. We know of no experiments which support the latter contention, but the whole question will be re-investigated so soon as opportunity permits. Another striking feature of the Phæophyceæ is the universal occurrence of fucosterol (IX) and total absence of sitosterol (VIII). This again sharply differentiates the Phæophyceæ both from other Classes of Algæ and from the Higher Plants. At the same time a connexion can be traced in so far as both fucosterol and sitosterol contain the same length of branched side-chain, fucosterol being a diethenoid member of the general phytosterol C_{29}-group (Heilbron, Phipers, and Wright, J., 1934, 1572; Coffey, Heilbron, and Spring, J., 1936, 738).

It is interesting to note that whereas in the Chlorophyceæ the chlorophyll components *a* and *b* are the same as in the Higher Plants, in the Phæophyceæ, Rhodophyceæ, Diatoms and Cyanophyceæ, chlorophyll *b* is absent (Seybold and Egle, *loc. cit.*) and therefore cannot be an integral factor in the photosynthetic process, unless one is to postulate a completely different mechanism for the Higher Plants and Green Algæ from that obtaining in other Classes.

The next Class to come under review is the Rhodophyceæ, whose members are mainly marine. The colour of these Red Seaweeds is not due solely to carotenoids but also to the presence of water-soluble red phycœrythrin and sometimes as well blue phycocyanin, both of which are pyrrole derivatives of the urobilin type. In general agreement with Kylin (1927, *loc. cit.*) we find carotene and lutein throughout all members of the seven Orders examined (Carter, Heilbron, and Lythgoe, *loc. cit.*). An unexpected abnormality has been observed in the case of *Polysiphonia nigrescens*, an alga of striking red-black colour. This definitely contains both fucoxanthin and fucosterol, whereas we have commonly found the sterol to be sitosterol in the other Rhodophyceæ which we have examined. This abnormality of pigment and sterol is curious, as *Polysiphonia nigrescens* is morphologically a perfectly normal diplobiontic member of the Ceramiales Order.

Another interesting group comprises the Myxophyceæ, also known as Cyanophyceæ or Blue-Green Algæ, a very ancient Class whose members inhabit both fresh and salt water and are among the simplest of plants, being devoid of sexuality, propagation being mainly by plain fission. Unlike all other Algæ, its members do not possess a proper chromatophore, the photosynthetic pigments being diffused through the outer layers of protoplasm. Myxophyceæ contain a specific carotenoid for which the name phycoxanthin was originally suggested by Kraus and Millardet in 1866. A more detailed examination of an alga of this Class (*Calothrix scopulorum*) was made by Kylin (1927, *loc. cit.*), who, using his capillary method, qualitatively noted carotene together with three other pigments to which he gave the names myxorhodin-α and -β and calorhodin. In 1935 Heilbron, Lythgoe, and Phipers (*Nature*, 1935, **136**, 989) isolated from *Rivularia nitida*, together with carotene and lutein, another carotenoid in crystalline form for which the name myxoxanthin was suggested. This alga is a terrestrial species, but the same pigment was obtained from a related marine species *Rivularia atra* and later a convenient source was found in the freshwater species *Oscillatoria rubrescens*, growing as a scum on one of the Hampton reservoirs of the Metropolitan Water Board. From this source, from which a substantial weight of alga was accumulated, a second new pigment, myxoxanthophyll, was also isolated, together with much carotene and lutein.

By employing micro-methods throughout, Heilbron and Lythgoe (J., 1936, 1376) were able to prove that myxoxanthin was a typical carotenoid monoketone having the formula $C_{40}H_{54}O$ and characterised by a single absorption band at 4880 A. It contains twelve ethenoid linkages and the carbonyl group must be conjugated with the chromophoric system, since the optical maximum of the oxime is displaced 100 A. nearer the violet end of the spectrum (compare Kuhn and Brockmann, *Ber.*, 1933, **66**, 828). Biological tests point to the presence of an unsubstituted β-ionone ring (vitamin A activity) and since the absorption spectrum of myxoxanthol, the aluminium *iso*propoxide reduction product, is identical with that of both γ-carotene and rubixanthin (eleven conjugated ethenoid linkages), the carbonyl group must be at the termination of such a conjugated system. From the fact that myxoxanthin, like astacene (*q. v.*), possesses only a single absorption band we conclude that its structure is (XI) rather than (XII), which would be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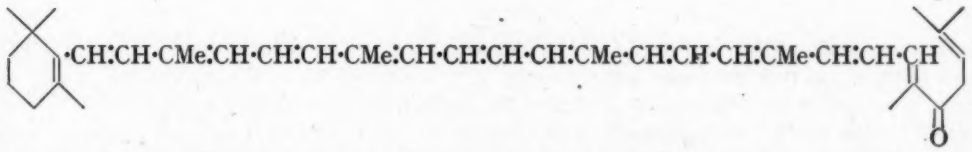
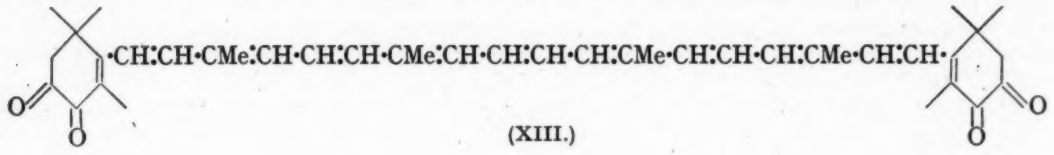

(XII.)

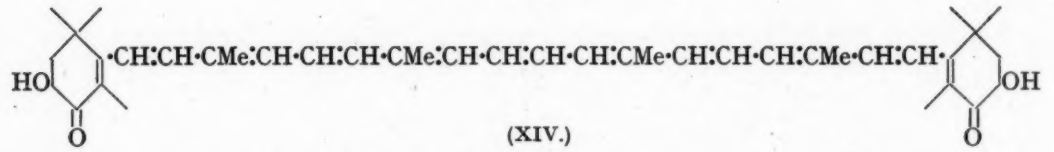
expected to exhibit the normal triplet spectrum. In the case of the hypophasic myxoxanthophyll the quantity of material available has unfortunately precluded a detailed examination, but analysis has given the formula $C_{40}H_{56}O_7$ (± 2H) and, from the tenacity with which it is retained by alumina in a column, it obviously contains a multiplicity of hydroxyl groups. Tischer (*Z. physiol. Chem.*, 1938, **251**, 109) has independently examined the carotenoids of another blue alga *Aphanizomenon flos-aquæ*, from which he isolated four pigments, principally an epiphasic lipochrome named aphanin and a hypophasic member, aphanizophyll. Of these, aphanin is seemingly isomeric with myxoxanthin, being according to Tischer (*Z. physiol. Chem.*, 1939, **260**, 257) derived from β-carotene and not from γ-carotene as is the case with myxoxanthin. Similarly aphanizophyll is considered by Tischer to be different from myxoxanthophyll, but further evidence is required before a definite decision can be reached. Whether future work establishes complete identity or not, it is abundantly clear that this Class synthesises a type of pigment which differentiates it quite sharply from other Algæ. Another striking feature is the complete absence of sterols (Carter, Heilbron, and Lythgoe, *loc. cit.*). Bearing in mind that in this Class there is a total lack of sexuality, the question as to whether any correlation exists between sterol content and sexuality naturally frames itself, and although no definite answer can at this stage be supplied it opens up an intriguing avenue for further investigation. If any connexion between sexual reproduction and the presence of sterols be ultimately established, the question of *Trentepohlia aurea*, of which mention has already been made, obviously needs reviewing on the botanical side. Whereas so far as is known this alga is sexually normal, it nevertheless is now growing in a habitat unusual for a green alga and moreover the genus is normally tropical. It may be that the disappearance of sterol under both the temperate and the terrestrial conditions forecasts an impending loss of sexuality. Some evidence in favour of this suggestion may be found in the case of *Pleurococcus Nægelii*. In this alga the only reproduction known is vegetative and although sterol has not altogether disappeared the quantity found was conspicuously small. Cognate to this question of sterol content and sexuality it is significant that the Bacteria which are also lacking in sexuality are likewise devoid of sterols.

Finally I would like to draw attention to the Euglenineæ, members of which are nearly all fresh-water and are sharply defined naked Flagellates of obscure origin which show a definite trend in the direction of animal organisation (Fritsch, *loc. cit.*). The chromatophores, when present, are bright green and not uncommonly members occur in such numbers as to give a characteristic coloration to the water. The Euglenineæ also possess saprophytic tendencies and it is somewhat doubtful whether the colourless forms should not be referred to the animal kingdom, as they have many characteristics of typical Protozoa. In addition to green Euglenineæ, members are known which are deep red (*e.g.*, *E. sanguinea*), the colour being due to the presence of the red pigment known to botanists as hæmatochrome (Cohn, *loc. cit.*). This pigment is also found in *Hæmatococcus pluvialis*, a member of the Volvocales belonging to the Green Algæ. Tischer (*Z. physiol. Chem.*, 1936, **239**, 257) has recently examined *Euglena heliorubescens*, which is rich in this red pigment, which he calls euglenarhodon. In addition chlorophylls *a* and *b*, β-carotene,

lutein, and zeaxanthin are present. According to Tischer, euglenarhodon is a tetraketone of formula $C_{40}H_{48}O_4$, isomeric with astacene, the typical Crustacean pigment first isolated in pure state by Kuhn and Lederer (*Ber.*, 1933, **66**, 488) and shown to have the structure (XIII). The same red pigment was also isolated by Tischer from the green alga *Hæmatococcus pluvialis* (*Z. physiol. Chem.*, 1937, **250**, 147; 1938, **252**, 225), but Kuhn, Stene, and Sörensen (*Ber.*, 1939, **72**, 1688) have independently examined it



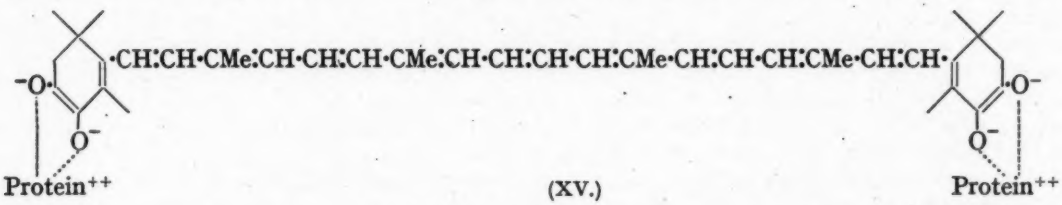
(XIII.)



(XIV.)

and proved that euglenarhodon and astacene are identical. Actually the natural pigment present in *Hæmatococcus pluvialis* is not astacene but an ester of a xanthophyll to which the name astaxanthin (XIV) is given, astacene being an artefact produced by aerial oxidation during hydrolysis.

Astaxanthin is also the natural pigment of the lobster, occurring in the form of an ester in the red epidermis, and in the green eggs it is present as the double enolate of β-carotene combined with protein (XV) (Kuhn and Sörensen, *Ber.*, 1938, **71**, 1879). The presence of astaxanthin in the Euglenineæ is of



(XV.)

much interest in view of the position occupied by these Flagellates in bridging the gap between the vegetable and the animal kingdom. Its occurrence in *Hæmatococcus pluvialis* is more difficult to comprehend; it may be noted, however, that the red pigment is apparently not present in the normal green motile Sphærella but only makes its appearance at the onset of the resting phase or with variation in constitution of its habitat. Apart from its occurrence in the Crustaceæ astaxanthin has also been found in many invertebrates and also in some of the lower vertebrates (Jones, *Ann. Reports*, 1940, **37**, 309). It has also been isolated from the retina of the hen (Wald and Zussmann, *J. Biol. Chem.*, 1938, **122**, 449), where its rôle is probably bound up with the process of colour vision, just as vitamin A is connected with this phenomenon in human vision. In this connexion the occurrence of eye-spots (stigmata) in nearly all motile cells of the Algæ merits attention. These appear as a reddish or brownish-red dot in the superficial layer of the cytoplasm and have for long been associated by botanists with hæmatochrome. In view of our more precise knowledge there can be little doubt that the pigment is astaxanthin.

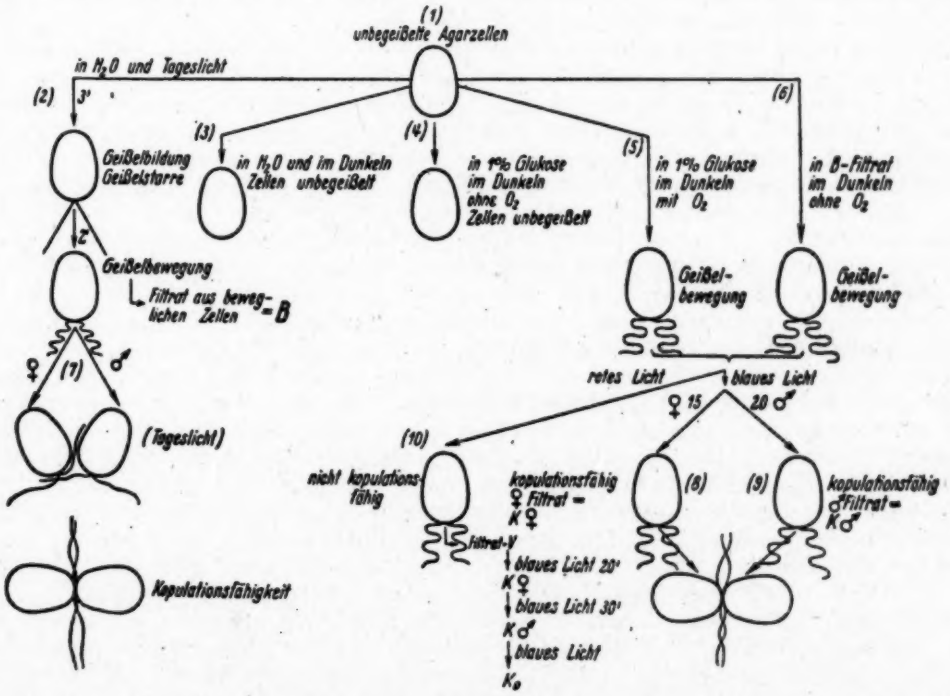
Reverting again to the lipoids of the Euglenineæ, Tischer (*Z. physiol. Chem.*, 1939, **259**, 163) states that he has isolated a small amount of ergosterol from *Euglena heliorubescens*. The evidence upon which this claim is based is somewhat slender but, if substantiated, further characterises this Class and links it with the Fungi.

In the foregoing, consideration has been centred upon pigmentation mainly in relation to the botanical classification of the Algæ with only incidental reference to any specific function of the respective pigments. I now wish to consider this functional aspect in some detail with special reference to the problem of sexual reproduction, the most fundamental of all physiological processes of the living organism.

One aspect of this problem has been examined during the past decade in great detail by the botanist F. Moewus, first at the Kaiser Wilhelm-Institut for Biology at Berlin and later in association with R. Kuhn at Heidelberg. It is beyond the scope of this lecture to do more than indicate in a general manner the extraordinarily important results which have been obtained by their joint efforts. For the purpose of their researches use was made in the first instance of the unicellular green alga *Chlamydomonas eugametos f. simplex* (Moewus, *Arch. Protistenkunde*, 1933, **80**, 469), in which male and female gametes

are morphologically identical (isogamous). The formation of their cilia, development of motility, and finally their ability to copulate is brought about under the influence of light. These three photochemical processes are illustrated in the diagram, which is reproduced from a paper published by Moewus (*Jahrb. wiss. Botanik*, 1938, **86**, 753).

The gametes are grown on an agar medium and under these conditions are devoid of cilia. If, however, they are suspended in distilled water and illuminated by light from a 150 watt lamp, cilia develop in the course of about three minutes and after irradiation for a further two minutes begin to oscillate and the cell becomes motile. The same effect can be brought about by keeping the algal suspension in the dark and in the presence of oxygen with the addition of 1% of glucose. Cane sugar is without action, but other disaccharides, of which gentiobiose is the most effective, can replace glucose. The formation of the cilia and the development of gamete motility can also be brought about by the addition of a cell-free filtrate of gametes which has already become motile in light to a suspension of a dark culture even in absence of oxygen. It follows from this that a definite chemical substance soluble in water and capable of producing motility has been produced by the action of light. This substance has been identified with almost complete certainty as the saffron pigment crocin, which has been shown to be effective in producing



motility in the amazing dilution of 1 : 250,000,000,000,000 (Kuhn, Moewus, and Jerchel, *Ber.*, 1938, **71**, 1541). The authors calculate that these figures imply that the activation of four sexual cells of *Chlamydomonas eugametos* is brought about by five molecules of crocin.

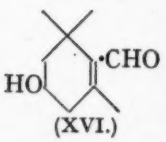
Even though the gametes have thus become motile, they are still not able to copulate and only acquire this property on further prolonged illumination. Whereas oscillation of the flagellæ is brought about in all parts of the visible spectrum, this second photochemical process is effected only by irradiation with blue or violet light, the active wave-lengths being the two mercury lines 4358 and 4961 A. Here again definite chemical substances are formed and discharged into the surrounding solution. This is shown by the fact that if a gamete suspension be suitably irradiated and filtered, copulation will ensue on addition of the filtrate to the appropriate unreactive "dark" gametes. The period of illumination is specific, being shorter for the female gametes than for the male, and over-irradiation gives only inactive filtrates. It is not essential for the formation of the copulatory materials to irradiate the sexual cells themselves with light of short wave-lengths. One can first illuminate a male or female cell suspension activated in the dark with glucose and oxygen with red light (6463 A.) for one hour and then filter and expose the inactive "red" filtrate (V) to the further action of short-wave light; the copulatory substances are then again formed. The time required for the assumption of female properties by the filtrate is from

20—30 minutes (K♀), after which it is no longer able to confer on female " dark " cells ability to copulate. After 60 minutes, however, the filtrate becomes able to render male " dark " cells active (K♂) and after 90 minutes' irradiation the filtrate (K_0) becomes permanently inactive.

Now all these phenomena can be exactly reproduced if in place of the filtrate (V) a light-sensitive pigment, *cis*-crocetin dimethyl ester (Kuhn and Winterstein, *Ber.*, 1933, **66**, 209), is employed. Under the influence of light this is converted gradually into the *trans*-form and it has been found that for this variety of *Chlamydomonas* the material conferring copulatory activity on the female " dark " gametes is a mixture of 3 parts of *cis*- and 1 part of *trans*-crocetin dimethyl ester and for the male " dark " gametes 3 parts of the *trans*-isomer and 1 part of the *cis*-ester. The V-material is thus the labile *cis*-crocetin dimethyl ester, and the K_0 material is the *trans*-isomer. It is only for this particular race of *Chlamydomonas* that the above ratios are effective; other species require different proportions of the two isomeric esters.

Although definite proof is lacking, it seems very probable that the dimethyl esters are actually the natural active materials, since it has been ascertained that a concentrated K_0 solution has exactly the same absorption bands as a solution of *trans*-crocetin dimethyl ester. The biological limit of activity of both esters is found at a dilution of 1 : 33,000,000,000; great as this is, it is not comparable with the effect of crocin in bringing about cell-motility.

In a still more recent memoir by Kuhn, Moewus, and Wendt (*Ber.*, 1939, **72**, 1702) considerable light is thrown upon the question of control of sex. For this purpose the hermaphroditic green alga *Chlamydomonas eugametos f. synoica* was selected. If this is treated by a filtrate of ♂-gametes of the dicœcious strain, all the cells become male, whereas a filtrate from ♀-gametes will render all the cells female. It is thus clear that here again the gametes secrete substances controlling sex. These sexual materials serving to determine sex among hermaphroditic organisms, and thus bestowing *primary* sexual characteristics, are called termones. Although the termones in the active filtrates have not so far been isolated, it has been ascertained that the male termone (androtermone) in contradistinction to the female termone (gynotermone) is volatile in steam and soluble in ether. By heating the solution containing the gynotermone with dilute sulphuric acid or with baryta water, its female characteristics are destroyed and simultaneously the solution acquires the male termone properties. This points to the relationship of gynotermone to androtermone being of the type glycoside to aglucone and the fact that, unlike glycosides in general, the female termone was hydrolysed by alkali led to the conclusion that it might be picrocrocin, which reacts similarly. This was experimentally verified by bringing *synoica*-cells into contact with a solution containing 0·02 μ of picrocrocin in 1 c.c. of water; after 10 minutes all the cells had become female towards ♂-gametes of the same race. If the picrocrocin solution is just heated with acid, safranal is formed and under its influence all the cells become male. Although the authors consider that safranal is identical with the natural androtermone, the corresponding gynotermone is shown to be 1000 times more active than picrocrocin and this they attribute to the presence of a sugar different from glucose, and possibly gentiobiose. More recently Kuhn and Löw * (*Ber.*, 1941, **74**, 219) report that 4-hydroxy*cyclo*citral (XVI) is also an androtermone like safranal. Perhaps the most outstanding feature of this brilliant series of investigations is the remarkable insight it provides of the versatile manner in which Nature utilises one substance only, the carotenoid crocin (or the as yet undetected *proto*-crocin) to carry out all the fundamental physiological sexual functions of these green Algæ. Kuhn and Moewus * (*Ber.*, 1940, **73**, 547) have adduced physiological, genetic, and chemical evidence of the general correctness of their views. They have shown, for example, that when crocin is secreted, picrocrocin is also secreted and vice versa; when non-motile mutants were obtained, they were unable to propagate sexually and lacked the ability to secrete crocin and picrocrocin or safranal. Again only in those physical circumstances (temperature range, incidence of light, etc.) when the cells are able to couple do they secrete their coupling gamones (*cis-trans* crocetin ester mixtures). It is suggested that the *cis* : *trans* ratios have a similar significance to the numerical relations between individual amino-acids in proteins. It seems certain that the cells directly produce the proper mixture and that this mixture does not arise by photochemical rearrangement of *cis*-ester (Kuhn and Moewus,* *Ber.*, 1940, **73**, 559). Finally, in this connection Kuhn (*Angew. Chem.*, 1940, **53**, 1) announces the existence of an enzyme in male gametes capable of effecting the fission of picrocrocin. This glycoside-splitting ferment is in all probability localised in the cell nucleus and this he considers may be a fundamental constituent of the chromosomes and indeed may be actually identical with the gene M (controlling masculinity).



(XVI.)

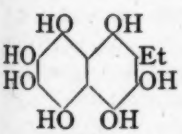
In *Chlamydomonas eugametos* we have been dealing with a species of Algæ where sexual reproduction

* This paper has unfortunately only been seen in the form of an abstract.

is isogamous, and I now wish to direct attention to an order of Algæ which reproduces oogamously and thus marks the highest stage in sexual reproduction. The members of the family Fucaceæ (Class phæophyceæ) reproduce in this manner by means of minute motile biciliate sperms and larger non-motile eggs.

The dicœcious members of the Fucales such as *Fucus serratus* are especially convenient to study, as large quantities of both male and female gametes can be obtained in a pure state and free from any possible contamination by gametes of the other sex. In the Fucaceæ the antheridia and oogonia are produced within flask-shaped sunken cavities, the conceptacles. These occur at the periphery of somewhat swollen and mucilaginous receptacles. The gradual extrusion of groups of mature sperms and eggs through the openings (ostioles) of the conceptacles normally occurs between the tides and is probably brought about in part by the expansion of mucilage together with contraction on desiccation. In Nature the gametes are removed from the surface of the conceptacles by the incoming tide and fertilisation thus takes place outside the parent plant. The numerous minute biciliated sperms contain a small yellowish chromatoplast and the mature antheridia therefore appear orange-yellow, which colour they impart to the entire receptacle. This affords a means of distinguishing the male plant in the dicœcious species of the Fuci at the time of gamete discharge. It seemed therefore of importance to determine experimentally the nature of the orange-yellow pigments characteristic of the sperm, as it appeared to us that such an investigation must inevitably throw light on this fundamental question of sexual reproduction. At the time this work was started by us (Carter, Cross, Heilbron, and Jones, unpublished work) we were not aware of the investigations of Kuhn and Moewus, and in any case the problem is different, as here only the male sperms are motile. Our experiments have been carried out with *Fucus serratus*, *Ascophyllum nodusum* and *Fucus vesiculosus* and have revealed that the pigment present in the male gametes consists almost entirely of β-carotene. In direct contrast to the results obtained with the male exudate the examination of the pigments of the corresponding female exudate has revealed that chlorophyll and fucoxanthin are responsible for the colour of the female ova. Unfortunately the advent of the war has so far prevented us from examining the respective gamete filtrates, but this we intend to do so soon as opportunity offers. In the meantime it would appear possible from the fact that β-carotene is to be observed mainly in the ♂-gametes that this carotenoid is bound up with their motility. It may be that under the influence of light and in presence of oxygen the hydrocarbon becomes partly oxidised to crocetin, which then acts as with *Chlamydomonas*. In support of this view Moewus (*Jahrb. wiss. Botanik*, 1938, **86**, 753) states that crude carotene extracted from both *Daucus carota* and green leaves, when exposed to light and air, gives an aqueous extract which acts in the same way as the female extract, but after longer standing in light the aqueous extract assumes the properties of the male copulatory substances. That carotene is utilised as a basis of physiologically active substances is familiar to all through its oxidative conversion into vitamin A in the animal body. The association of carotene with sexual processes is further illustrated in another direction by recent work carried out by Emerson and Fox (*Proc. Roy. Soc.*, 1940, *B*, **128**, 275) on the aquatic fungus *Allomyces*. These authors have observed that the orange colour of the motile male gametes in the sexual phase is due to γ-carotene present in high concentration.

Another problem to be elucidated in connexion with the sexual process in these Fucaceæ is the mechanism whereby the motile ♂-gametes become attracted to the egg. Kuhn and Wallenfels (*Ber.*, 1939, **72**, 1407) have shown that in the case of the sea-urchin, the ova secrete a definite compound, echinochrome A, into the sea-water which immediately attracts the sperms. The pigment is a quinone derived from leuco-echinochrome A (XVII) and although the mechanism of excitation is still unknown, it is suggested that, as echinochrome is a pigment of known redox potential, it may function as a typical co-ferment. It may be that fucoxanthin plays a similar rôle in these algal ova or that something akin to echinochrome is secreted. The latter possibility is supported by the fact that we have obtained cell-free extracts of ova of *Fucus serratus* which attract the sperms. This is the problem upon which in normal times we should have hoped to be working, but this, with other fascinating questions of like nature and interest, has had to be set aside for the time being in favour of investigations more relevant to the great struggle on behalf of the defence of civilisation.



(XVII.)

17. *Organic Sulphur Compounds. Part XXVII. The Relation between the Constitution of Thioethers and Thiols and their Sensitivity towards Alkali.*

By Alexander Schönberg and Youssef Iskander.

Whereas the thioethers listed in Table I are remarkably stable towards alkali, the nitro-derivatives (Table II) are extremely sensitive. The latter compounds are all characterised by the group p-$NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}SR$ or by such groups in which the hydrogen in the methylene group is partially or completely substituted. The mechanism of the hydrolysis is discussed (schemes A and B). *Didesyl sulphide* (XII) was obtained in two isomeric forms. Both are very sensitive towards alkali (scheme C); the same is true of *desylthiol* (XIV) (scheme F). As may be seen from schemes F and D, it is believed that the action of alkali on β-keto-thiols, the corresponding thioethers, and β-ketothiocarboxylic acids, which are highly sensitive to alkali, proceeds in such a way that water or the alkali hydroxide is added to the carbonyl group, and the hydrate so formed decomposes. There is no general parallelism between thermolability of thioethers and their sensitivity towards alkali, since the thermolabile phenyl triphenylmethyl sulphide is very stable towards alkali; on the other hand, didesyl sulphide is thermolabile (formation of the blue thiobenzil; scheme E) and is also very sensitive to alkali.

Dimethyl sulphide is only partially hydrolysed when heated with 3N-alkali at 260° for two hours (Billheimer and Reid, *J. Amer. Chem. Soc.*, 1930, **52**, 4338), but two classes of its derivatives, the β- and the γ-ketothio-carboxylic acids, are very sensitive to the action of alkali (Nicolet, *J. Amer. Chem. Soc.*, 1931, **53**, 3067; Behaghel and Ratz, *Ber.*, 1939, **72**, 1257), the former undergoing hydrolysis and the latter decomposition:

$$Ph{\cdot}CO{\cdot}CHPh{\cdot}S{\cdot}CH_2{\cdot}CO_2H \xrightarrow{H_2O} Ph{\cdot}CO{\cdot}CH_2Ph + OH{\cdot}S{\cdot}CH_2{\cdot}CO_2H$$

$$Ph{\cdot}CO{\cdot}CH_2{\cdot}CHPh{\cdot}S{\cdot}CH_2{\cdot}CO_2H \longrightarrow Ph{\cdot}CO{\cdot}CH{:}CHPh + SH{\cdot}CH_2{\cdot}CO_2H$$

This paper deals with p-nitrobenzyl thioethers (Table II), one ββ′-diketo-thioether (XII) and the corresponding thiol (XIV), which are all highly sensitive to alkali.

Part I.

Sensitivity of p-*Nitrobenzyl Thioethers towards Alkali.*—In Table I are listed a number of substances which, according to our observation, are affected either only slightly or not at all by 1 hour's boiling in 5% alkali solution, in which they are all soluble. In contrast, the substances listed in Table II are completely or almost completely hydrolysed when heated for 5 minutes in 5% alkali solution, in which they are all soluble.

Table I.

(I.) $CH_2Ph{\cdot}S{\cdot}CH_2{\cdot}CO_2H$ [1] $\quad$ p-$NH_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$ (II.)

(III.) $CH_2Ph{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ $\quad$ $CPh_3{\cdot}S{\cdot}CH_2{\cdot}CO_2H$ [2] (IV.)

Table II.

(V.) p-$NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$ $\quad$ p-$NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ (VI.)

(VII.) p-$NO_2{\cdot}C_6H_4{\cdot}CPh_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$

[1] Holmberg, *J. pr. Chem.*, 1934, **141**, 93. [2] Bülmann and Due, *Bull. Soc. chim.*, 1924, **35**, 384.

Mechanism of the Action of Alkali on the p-*Nitrobenzyl Thioethers.*—For the action of alkali on α-(p-*nitrotriphenylmethylthio*)*acetic acid* (VII), the following scheme is proposed, which shows the addition of sodium hydroxide to the nitro-group, the splitting off of sulphenacetic acid (VIII), and the rearrangement of the remainder to p-nitrotriphenylmethane (IX), which separates during the reaction:

(A) (VII.) $NO_2{\cdot}C_6H_4{\cdot}CPh_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H \xrightarrow{NaOH} OH{\cdot}NO(ONa){\cdot}C_6H_4{\cdot}CPh_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H \longrightarrow$

(VIII.) $ONa{\cdot}S{\cdot}CH_2{\cdot}CO_2H + OH{\cdot}NO{:}C_6H_4{:}CPh_2 \longrightarrow NO_2{\cdot}C_6H_4{\cdot}CHPh_2$ (IX.)

For the saponification of α-(p-*nitrobenzylthio*)*acetic acid* (V), the following scheme, in contrast to the above (saponification of VII), shows as first step, not the addition of sodium hydroxide to the nitro-group, but the formation of a sodium salt of the *aci*-nitro-group. (X) indicates, but only very roughly, an unstable intermediate product. The final product, azobenzaldehyde (XI), separates during the reaction:

(B) $2p$-$NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$ (V.) $\xrightarrow{NaOH} 2NO(ONa){:}C_6H_4{:}CH{\cdot}S{\cdot}CH_2{\cdot}CO_2H \longrightarrow$

$$(VIII) + \left[\begin{array}{c} | \\ 2ON{:}C_6H_4{:}CH \\ | \end{array}\right] (X.) \longrightarrow CHO{\cdot}C_6H_4{\cdot}N{:}N{\cdot}C_6H_4{\cdot}CHO \quad (XI.)$$

Sulphenacetic acid (VIII), which should be formed according to the above scheme, was not isolated, as this substance is very unstable towards alkali. The alkaline solution, after acidification, furnished hydrogen sulphide, which is one of the products of the action of alkali on sulphenacetic acid (Schöberl, *Annalen*, 1933, **507**, 111).

It is suggested that the action of alkali on β-(p-*nitrobenzylthio*)*propionic acid* (VI) is like that on *p*-nitrobenzylthioacetic acid, and one would expect *p*-azobenzaldehyde together with β-sulphenpropionic acid ($OH{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$) to be formed. We obtained the azobenzaldehyde in a very small yield and *p*-azoxybenzaldehyde ($CHO{\cdot}C_6H_4{\cdot}NO{:}N{\cdot}C_6H_4{\cdot}CHO$) and β-dithiodipropionic acid

($CO_2H{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$)

in good yield. The formation of the azoxy-compound is explained by the suggestion that the azo-compound first formed is oxidised by the β-sulphenpropionic acid, which in turn is reduced to β-dithiodipropionic acid (compare Price and Twiss, J., 1910, **97**, 1175; Fries, *Ber.*, 1912, **45**, 2965).

Part II.

The Action of Alkali on ββ'-Diketo-sulphides, β-Ketothio-carboxylic Acids and β-Keto-thiols.—(1) *Action of alkali on didesyl sulphide* (XII). This substance occurs in two probably stereoisomeric forms, which are completely or almost completely hydrolysed by aqueous alcoholic alkali (3%) after 5 minutes' boiling, deoxybenzoin and, after acidification, sulphur being obtained:

$$\text{(C)}\quad \text{(XII.)}\quad Ph{\cdot}CO{\cdot}CHPh{\cdot}S{\cdot}CHPh{\cdot}COPh + 2H_2O \longrightarrow 2Ph{\cdot}CO{\cdot}CH_2Ph + S(OH)_2$$

$$2S(OH)_2 \longrightarrow H_2O + H_2S_2O_3 \xrightarrow{\text{acid}} H_2SO_3 + S$$

[With regard to the decomposition of $S(OH)_2$, see Förster, Lange, Drossbach, and Seidel, *Z. anorg. Chem.*, 1923, **128**, 268.]

(2) *Mechanism of the action of alkali on β-ketothio-carboxylic acids and ββ'-diketo-sulphides.* It is suggested that the first step is the formation of a hydrate, which is decomposed in accordance with scheme D (A and B are univalent groups; in the case of β-ketothio-carboxylic acids, R is an aliphatic acid group, *e.g.*, $CH_2{\cdot}CO_2H$):

$$\text{(D)}\quad R'{\cdot}CO{\cdot}CAB{\cdot}SR \longrightarrow R'{\cdot}C(OH)_2{\cdot}CAB{\cdot}SR \longrightarrow OH{\cdot}SR + R'{\cdot}C(OH){:}CAB \longrightarrow R'{\cdot}CO{\cdot}CHAB$$

According to this suggestion the degree of susceptibility towards alkali of sulphides which have a carbonyl group in the β-position depends on the tendency to form hydrates and on their instability, *i.e.*, on the velocity of the decomposition reaction.

The fission of α-(benzoylbenzhydrylthio)acetic acid (XIII) by alkali in two different directions (Behaghel and Ratz, *Ber.*, 1939, **72**, 1275) may also be explained by hydrate formation:

$$Ph{\cdot}CO{\cdot}CPh_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H \longrightarrow Ph{\cdot}C(OH)_2{\cdot}CPh_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H \begin{cases} \xrightarrow{a} Ph{\cdot}CO{\cdot}CHPh_2 + OH{\cdot}S{\cdot}CH_2{\cdot}CO_2H \\ \xrightarrow{b} Ph{\cdot}CO_2H + CHPh_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H \end{cases}$$

(XIII.)

Scheme *b* resembles the cleavage of a non-enolisable ketone by the action of sodamide (Schönberg, *Annalen*, 1924, **436**, 206):

$$COPh_2 + NaNH_2 \longrightarrow CPh_2(ONa){\cdot}NH_2 \xrightarrow{\text{decomp.}} PhH + Ph{\cdot}CO{\cdot}NHNa.$$

In the case of (XIII), the formation of deoxybenzoin (scheme *a*) is the main reaction. On the other hand, β-(*benzoylbenzhydrylthio*)*propionic acid*, $Ph{\cdot}CO{\cdot}CPh_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, and *phenyl α-benzoylbenzhydryl sulphide*, $Ph{\cdot}CO{\cdot}CPh_2{\cdot}SPh$, yield mainly β-(*benzhydrylthio*)*propionic acid*, $CHPh_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, and phenyl benzhydryl sulphide, $CHPh_2{\cdot}SPh$, respectively, in accordance with scheme *b*.

(3) *Relationship between thermolability of thioethers and sensitivity towards alkali.* There is no general parallelism. For instance, phenyl triphenylmethyl sulphide is rather unstable towards heat (decomposition into diphenyl disulphide and triphenylmethyl; Schönberg and co-workers, *Ber.*, 1929, **62**, 2552), but is completely or almost completely resistant to boiling with aqueous-alcoholic alkali (5%) for four hours. On the other hand, either of the two stereoisomeric forms of didesyl sulphide (XII) decomposes above its melting point with formation of a blue compound, believed to be thiobenzil (Schönberg and Schütz, *Annalen*, 1927, **454**, 53):

$$\text{(E)}\quad Ph{\cdot}CO{\cdot}CHPh{\cdot}S{\cdot}CHPh{\cdot}COPh \longrightarrow Ph{\cdot}CO{\cdot}CSPh + Ph{\cdot}CH_2{\cdot}COPh$$

Saponification of (XII) yields benzilic acid as a by-product, produced probably by the benzilic acid rearrangement of thiobenzil.

(4) *Action of alkali on β-keto-thiols.* The action of alkali on β-keto-thiols whereby the thiol group is easily replaced by hydrogen with the liberation of sulphur, observed by Groth (*Chem. Zentr.*, 1924, I, 1038) in the case of phenacylthiol, was observed by us when *desylthiol* (XIV) or its *benzoate* was heated with 2·5% alcoholic alkali for 10 minutes, giving deoxybenzoin and, after acidification, sulphur. Scheme F shows the analogy with the action of alkali on thioethers (see above).*

(F) $\underset{\text{(XIV.)}}{\text{Ph·CO·CHPh·SH}} \xrightarrow{H_2O} \text{Ph·C(OH)}_2\text{·CHPh·SH} \longrightarrow \text{Ph·CO·CH}_2\text{Ph} + \text{SH·OH} \longrightarrow \text{H}_2\text{O} + \text{S}.$

On the other hand, *α-benzoylbenzhydrylthiol* (XV) is more stable to alkali than (XIV), since it can be prepared in good yield by the action of alkali on the corresponding *thiobenzoate* (XVI):

$$\text{Ph·CO·CPh}_2\text{·S·COPh (XVI)} \xrightarrow{H_2O} \text{Ph·CO·CPh}_2\text{·SH (XV)} + \text{Ph·CO}_2\text{H}$$

Experimental.

Part I.

α-(p-*Nitrobenzylthio*)*acetic Acid* (V).—*p*-Nitrobenzyl chloride (4·3 g.), dissolved in alcohol (100 c.c.), was treated with a solution of thiolacetic acid (2·5 g.) and sodium bicarbonate (5 g.) in water (20 c.c.) and the mixture boiled on the water-bath for 1 hour. Cooling, dilution with water, filtration, and acidification gave a colourless crystalline *acid* (4·5 g.), which separated from dilute alcohol or carbon tetrachloride in colourless scales, m. p. 114° (Found: C, 48·1; H, 3·7; N, 6·3; S, 14·1. $C_9H_9O_4NS$ requires C, 47·6; H, 4·0; N, 6·2; S, 14·1%).

Alkaline hydrolysis. The acid (2 g.) was dissolved in 5% sodium hydroxide solution (50 c.c.) and boiled for 5 minutes. The solid obtained (1·1 g.) was washed with water and crystallised from glacial acetic acid, giving orange-red crystals, m. p. 230—235° alone or mixed with *p*-azobenzaldehyde (Freundler, *Bull. Soc. chim.*, 1904, **31**, 453) (Found: C, 70·3; H, 4·2; N, 11·9. Calc. for $C_{14}H_{10}O_2N_2$: C, 70·5; H, 4·2; N, 11·8%). On acidification of the alkaline filtrate, hydrogen sulphide was evolved.

β-(p-*Nitrobenzylthio*)*propionic Acid* (VI).—Prepared from *p*-nitrobenzyl chloride (4·3 g.) and β-thiolpropionic acid (2·7 g.) by the method described above, and isolated in a similar way, the *acid* (4·5 g.) crystallised from dilute alcohol in colourless needles, m. p. 104—105° (Found: C, 50·0; H, 4·6; N, 5·8; S, 13·5. $C_{10}H_{11}O_4NS$ requires C, 49·8; H, 4·6; N, 5·8; S, 13·3%).

Alkaline hydrolysis. The acid (2 g.) was hydrolysed as described above. The solid obtained (1·1 g.) crystallised from benzene in yellow needles, m. p. 190° alone or mixed with *p*-azoxybenzaldehyde (Human and Weil, *Ber.*, 1903, **36**, 3474) (Found: C, 66·1; H, 3·9; N, 11·0. Calc. for $C_{14}H_{10}O_3N_2$: C, 66·1; H, 3·9; N, 11·0%). On acidification of the alkaline filtrate, hydrogen sulphide was not evolved and a dark solid was slowly precipitated. This was collected, dried, boiled with carbon tetrachloride to remove any unchanged acid, and crystallised from hot water, giving β-dithiodipropionic acid, m. p. 155° alone or mixed with an authentic specimen (Biilmann, *Annalen*, 1905, **339**, 365).

The acids (V) and (VI) were completely hydrolysed in 5% sodium hydroxide solution in 24 hours at room temperature.

α-(p-*Nitrotriphenylmethylthio*)*acetic Acid* (VII).—*p*-Nitrotriphenylchloromethane (3·5 g.), dissolved in dry toluene (30 c.c.), was treated with thiolacetic acid (1 g.), and the solution boiled for 1 hour until no more hydrogen chloride was evolved. Ether (30 c.c.) was added, and the p-*nitrotriphenylmethylthioacetic acid* extracted with sodium bicarbonate solution. The viscous acid (3·6 g.) obtained on acidification solidified over-night in the ice chest and separated from benzene–light petroleum (b. p. 60—70°) in colourless crystals, m. p. 153—155° (Found: C, 65·7; H, 4·4; N, 3·9. $C_{21}H_{17}O_4NS$ requires C, 66·5; H, 4·5; N, 3·7%).

Alkaline hydrolysis. The acid (0·34 g.) was treated with 5% sodium hydroxide solution (20 c.c.) in the cold with the formation of a yellow solid (probably the sodium salt). After 5 minutes' boiling, the liberated oily substance was extracted from the red liquid with ether and proved to be *p*-nitrotriphenylmethane (0·26 g.), m. p. 97°, not depressed by an authentic specimen, m. p. 94° (Baeyer and Lohr, *Ber.*, 1890, **23**, 1622). Acidification of the alkaline liquid gave much hydrogen sulphide.

α-(p-*Aminobenzylthio*)*acetic Acid* (II).—α-(*p*-Nitrobenzylthio)acetic acid (1·5 g.) was heated with concentrated hydrochloric acid (10 c.c.) and granulated tin (3 g.) on the water-bath until all the tin had dissolved. The excess of hydrochloric acid was evaporated on the water-bath, the viscous residue dissolved in water (100 c.c.) and freed from tin with hydrogen sulphide, and the clear filtrate evaporated to dryness on the water-bath. The residual hydrochloride was dissolved in the minimum amount of cold water, and the filtered solution treated with a few drops of aqueous ammonia. While the solution was still very faintly acid to litmus

* An analogous scheme is proposed for the quantitative and quick replacement of the bromine by hydrogen when α-benzoylbenzhydryl bromide is heated with hydrogen bromide in acetic acid (Löwenbein and Schuster, *Annalen*, 1930, **481**, 117):

$$\text{Ph·CO·CBrPh}_2 + \text{HBr} \longrightarrow \text{Ph·CBr(OH)·CBrPh}_2 \longrightarrow \text{Br}_2 + \text{Ph·C(OH):CPh}_2 \longrightarrow \text{Ph·CO·CHPh}_2$$

the *amino-acid* was precipitated; it separated from alcohol in colourless crystals, m. p. 155—156°, soluble in water and alcohol and, with difficulty, in ether and benzene (Found: C, 55·1; H, 5·4; N, 6·7; S, 16·2. $C_9H_{11}O_2NS$ requires C, 54·8; H, 5·6; N, 7·1; S, 16·2%). The acid was recovered unchanged after 20 minutes' boiling with 5% sodium hydroxide solution. On diazotisation and coupling with β-naphthol it gave a dark red dye.

Part II.

β-(*Benzylthio*)*propionic Acid* (III).—Benzyl chloride (2·53 g.), dissolved in alcohol (50 c.c.), was treated with a solution of β-thiolpropionic acid (2·1 g.) and sodium bicarbonate (4 g.) in water (20 c.c.), and the mixture boiled on the water-bath for 1 hour. Cooling, dilution with water, washing with ether, and acidification gave an oily acid (3·5 g.), which solidified in the ice-chest. It crystallised from light petroleum (b. p. 60—70°) in colourless plates, m. p. 82—83° (Mörner, *Z. physiol. Chem.*, 1904, **42**, 352, gives m. p. 81·5°). The acid was recovered almost unchanged after 1 hour's boiling with 5% sodium hydroxide solution.

Desylthiol (XIV).—A solution of sodium (2·3 g.) in absolute alcohol (100 c.c.) was treated with excess of hydrogen sulphide for 1 hour at room temperature. The sodium hydrosulphide solution was cooled in ice and treated with finely powdered desyl chloride (23 g.) (*Organic Syntheses*, 1932, **12**, 20) in one addition. A quick reaction occurred with the formation of a colourless microcrystallline solid (11·5 g., m. p. 120—140°) mixed with sodium chloride. The alcoholic filtrate was diluted with ice-water, the liberated oily substance extracted with ether, and the ethereal layer dried over calcium chloride for 1 day. After distillation of the ether the viscous oily residue (11 g.) gave the thiol test (solid sodium nitrite, added to a solution of the thiol in glacial acetic acid, gave a red coloration; Rheinboldt, *Ber.*, 1927, **60**, 184). The lead salt of the thiol was precipitated from ethereal solution by lead acetate, washed with ether, and decomposed with dilute hydrochloric acid. The liberated thiol, isolated by means of ether, solidified in the ice-chest after 1 month. On treatment with a few c.c. of cold alcohol, half the bulk, which was semi-solid, was dissolved, leaving a colourless crystalline solid, m. p. 42—44° (Found: C, 73·8; H, 5·4; S, 13·8. $C_{14}H_{12}OS$ requires C, 73·7; H, 5·3; S, 14·0%). A solution of the thiol in alcohol reacted with iodine in potassium iodide; the expected disulphide could not be obtained crystalline.

Alkaline hydrolysis. The thiol (2 g.), dissolved in alcohol (60 c.c.), was treated with 10% sodium hydroxide solution (20 c.c.), and the mixture boiled for 10 minutes. Dilution with ice-water precipitated deoxybenzoin (1·2 g.), m. p. 58—60°; the filtrate, on acidification, gave hydrogen sulphide and a yellowish-white emulsion, which was extracted with ether. Evaporation of the ether left sulphur (0·2 g.), m. p. 118—120° after being washed with alcohol.

Desyl Thiobenzoate.—(1) A solution of desyl chloride (17·4 g.) and potassium thiobenzoate (Kym, *Ber.*, 1899, **32**, 3533) (13·4 g.) in absolute alcohol (400 c.c.) was boiled for 10 minutes, potassium chloride being precipitated. After cooling, a colourless crystalline substance separated, which was washed with water and recrystallised from alcohol. Yield 25 g., m. p. 110—112° (Found: C, 75·9; H, 5·0; S, 9·6. $C_{21}H_{16}O_2S$ requires C, 75·9; H, 4·8; S, 9·6%).

(2) Desylthiol (0·5 g.), dissolved in pyridine (2 c.c.), was treated with benzoyl chloride (0·25 c.c.); after 5 minutes, the mixture was cooled and acidified with cold dilute sulphuric acid. The liberated oily substance, after decantation from the aqueous layer, was treated with hot alcohol; on cooling, a crystalline solid (0·5 g.) was precipitated, m. p. 110—112° alone or mixed with the *desyl thiobenzoate* prepared by method (1).

Alkaline hydrolysis. Desyl thiobenzoate (10 g.), dissolved in boiling alcohol (300 c.c.), was treated with 10% sodium hydroxide solution (100 c.c.) and boiled for 5 minutes. Ice-water was then added; the precipitated deoxybenzoin (5·2 g.) was removed, the filtrate acidified and extracted with ether, and the ethereal layer washed with sodium bicarbonate solution. The bicarbonate layer, after acidification, gave benzoic acid and hydrogen sulphide; the ether contained about 1 g. of a viscous liquid contaminated with a yellow solid, which was isolated by the addition of alcohol. It crystallised from benzene–absolute alcohol, and proved to be sulphur, m. p. 118—120°.

Didesyl Sulphide (XII).—The solid, m. p. 120—140°, obtained in the preparation of desylthiol (see above) separated from benzene–absolute alcohol in colourless needles (5·5 g.), m. p. 168—169° (Found: C, 79·9; H, 5·3; S, 7·6. $C_{28}H_{22}O_2S$ requires C, 79·6; H, 5·2; S, 7·6%). The mother-liquor, after concentration and evaporation of the benzene, deposited a substance (4·5 g.), which crystallised from absolute alcohol in long colourless needles, m. p. 128—129° (Found: C, 79·5; H, 5·3; S, 7·7%). The two substances are both *didesyl sulphide*; it is suggested that one of them is the racemic form, and the other, the *meso*-form. Both forms were partly dissolved in hot alcohol; after cooling, the supersaturated solutions were immediately treated with a few drops of 10% sodium hydroxide solution. An immediate yellow or orange colour (according to concentration) was developed. Both forms, when heated above the m. p., gave a blue melt (formation of thiobenzil; Schönberg and Schütz, *Annalen*, 1927, **454**, 53).

Alkaline hydrolysis. Didesyl sulphide (4 g.), m. p. 169°, dissolved in boiling alcohol (100 c.c.), was treated with 10% sodium hydroxide solution (40 c.c.) and boiled for 5 minutes. When ice-water was added in excess, deoxybenzoin (2·9 g.) was precipitated. The filtrate was acidified, and the liberated oily substance extracted with ether; sodium bicarbonate removed benzilic acid from the extract. The ether, after evaporation, left a viscous oily substance contaminated with sulphur, which was separated by washing with alcohol.

The same result was obtained by the hydrolysis of the form, m. p. 129°.

β-(*Desylthio*)*propionic Acid.*—Desyl chloride (4·6 g.) and β-thiolpropionic acid (2·1 g.) were heated on the water-bath for 6 hours until no more hydrogen chloride was evolved. The addition of benzene caused the precipitation of β-dithiodipropionic acid, m. p. 155°. A few c.c. of petroleum (b. p. 60—70°) were added to the filtrate, and the β-(*desylthio*)*propionic acid* extracted with sodium bicarbonate solution. Acidification of the bicarbonate layer liberated the acid as an oil which solidified on standing; it crystallised from dilute methyl alcohol in micro-needles, m. p. 108—109° (Found: C, 68·0; H, 5·5; S, 10·9. $C_{17}H_{16}O_3S$ requires C, 68·0; H, 5·3; S, 10·7%).

Comparative Experiment on the Hydrolysis of α-(*Desylthio*)*acetic Acid and* β-(*Desylthio*)*propionic Acid.*—The two acids (0·2 g. of each) in two test tubes were each treated with 5% sodium hydroxide solution (5 c.c.) and heated on the water-bath. Ths solution of desylthioacetic acid became turbid even in the cold, that of the other acid only after 3·5 minutes; the heating was then stopped, and the products immediately cooled. The first turbid solution deposited deoxybenzoin (compare Behaghel and Schneider, *Ber.*, 1935, **68**, 1588). The other alkaline solution, on acidification, gave β-(desylthio)propionic acid in almost quantitative yield. Treatment of this acid with the hot sodium hydroxide solution for 20 minutes caused partial hydrolysis (about 15%), with the formation of deoxybenzoin.

Desyl Phenyl Sulphide.—Desyl chloride (4·6 g.) was added to an alcoholic solution of thiophenol (2·2 g.) and sodium ethoxide (0·46 g. of sodium in 20 c.c. of absolute alcohol); the mixture was boiled for 10 minutes. Water in sufficient amount to dissolve the precipitated sodium chloride was added, and the mixture cooled in ice; desyl phenyl sulphide was precipitated in good yield. It crystallised from petroleum (b. p. 60—70°) in long colourless needles, m. p. 83—84° (Found: C, 78·9; H, 5·4; S, 10·5. Calc. for $C_{20}H_{16}OS$: C, 78·9; H, 5·3; S, 10·5%) (Mitchell and Smiles, J., 1933, 1529, give m. p. 81°).

Alkaline hydrolysis. Desyl phenyl sulphide (0·5 g.), dissolved in hot alcohol (50 c.c.), was treated with 10% sodium hydroxide solution (5 c.c.) and boiled for ½ hour. The mixture was cooled, diluted with water, and extracted with ether. When the alkaline solution was acidified, a strong smell of thiophenol was noticed; the ether contained most of the original substance.

α-*Benzoylbenzhydryl Thiobenzoate* (XVI).—Benzoyldiphenylchloromethane (Löwenbein and Schuster, *Annalen*, 1930, **481**, 114) (10·2 g.), dissolved in boiling absolute alcohol (100 c.c.), was treated with potassium thiobenzoate (5·9 g.) (compare Kym, *loc. cit.*) in absolute alcohol (100 c.c.) and boiled for 10 minutes. Sufficient water to dissolve the potassium chloride was added; on cooling, an oily substance was precipitated which solidified on standing. It separated from absolute alcohol in colourless crystals (5 g.), m. p. 129—130° (Found: C, 79·3; H, 5·1; S, 7·9. $C_{27}H_{20}O_2S$ requires C, 79·4; H, 4·9; S, 7·8%).

α-*Benzoylbenzhydrylthiol* (XV).—α-Benzoylbenzhydryl thiobenzoate (20 g.), dissolved in boiling alcohol (200 c.c.), was treated with 10% sodium hydroxide solution (150 c.c.) and boiled for 10 minutes. The dark yellow solution was cooled, diluted with water, and extracted with ether. The alkaline solution was acidified, and the liberated oily substance extracted with ether. The ethereal layer was washed with sodium bicarbonate solution; acidification of the bicarbonate washings liberated benzoic acid. The ether contained an oily substance which solidified at once (yield, 9 g.); it separated from dilute alcohol in micro-needles, m. p. 98—101°. The thiol test gave a red coloration (Found: C, 78·6; H, 5·5; S, 10·3. $C_{20}H_{16}OS$ requires C, 78·9; H, 5·3; S, 10·5%).

*Di-*α*-benzoylbenzhydryl Disulphide.*—α-Benzoylbenzhydrylthiol, dissolved in the necessary amount of hot acetic acid, was treated with the equivalent amount of ferric chloride solution and boiled for 10 minutes. On cooling, a colourless amorphous solid was precipitated; it separated from chloroform–alcohol or from much absolute alcohol in colourless crystals, m. p. 150—154° (Found: C, 79·2; H, 4·9; S, 10·5. $C_{40}H_{30}O_2S_2$ requires C, 79·2; H, 4·9; S, 10·6%).

α-(*Benzoylbenzhydrylthio*)*acetic Acid* (XIII).—Benzoyldiphenylchloromethane (15·3 g.) was treated with thiolacetic acid (4·6 g.) and heated on the water-bath for 2 hours until no more hydrogen chloride was evolved. Dry benzene was added and a few c.c. of petroleum (b. p. 60—70°), causing a slight precipitation of dithiodiacetic acid, m. p. 108°. From the filtrate, a few crystals of benzoyldiphenylmethane, m. p. 136°, separated overnight; these were removed, and (XIII) extracted with sodium bicarbonate solution. Acidification liberated the acid as a viscous oil, which crystallised from benzene–petroleum (b. p. 60—70°) in large particles, m. p. 132—134°; it was recrystallised from dilute alcohol (Found: C, 72·9; H, 5·2; S, 8·8. Calc. for $C_{22}H_{18}O_3S$: C, 72·9; H, 5·0; S, 8·8%).

Behaghel and Ratz (*Ber.*, 1939, **72**, 1275) found that the alkaline hydrolysis of (XIII) gave α-(benzhydrylthio)acetic acid; they gave the m. p. as 218° (probably a misprint for 128°, the correct m. p.).

β-(*Benzoylbenzhydrylthio*)*propionic Acid.*—Benzoyldiphenylchloromethane (9·2 g.) and β-thiolpropionic acid (3·2 g.) were heated on the water-bath for 6 hours until no more hydrogen chloride was evolved. After cooling, the addition of ether precipitated β-dithiodipropionic acid, m. p. 155°. β-(*Benzoylbenzhydrylthio*)-*propionic acid* was extracted from the ethereal solution with sodium bicarbonate solution and liberated on acidification as a viscous substance which solidified after decantation of the aqueous layer and treatment with 50% methyl alcohol. It crystallised from dilute methyl alcohol in small scales, m. p. 134—136° (Found: C, 73·5; H, 5·2; S, 8·6. $C_{23}H_{20}O_3S$ requires C, 73·4; H, 5·3; S, 8·5%).

Alkaline hydrolysis. The acid was boiled with 7% sodium hydroxide solution for 20 minutes. On cooling and dilution with water, a minute quantity of substance was precipitated. This was removed, and acidification of the filtrate gave a substance, which separated from dilute alcohol in colourless crystals of β-(*benzhydrylthio*)*propionic acid*, m. p. 89—90° (Found: C, 70·8; H, 6·2; S, 12·0. $C_{16}H_{16}O_2S$ requires C, 70·6; H, 5·9; S, 11·8%).

Phenyl α-Benzoylbenzhydryl Sulphide.—Benzoyldiphenylchloromethane (3·07 g.) and thiophenol (1·1 g.) in dry toluene (20 c.c.) were boiled for 1 hour until no more hydrogen chloride was evolved. Most of the toluene was distilled off under reduced pressure, and light petroleum (b. p. 50—60°) and a few c.c. of benzene added. After cooling in the ice-chest for some time, a colourless solid was precipitated, which separated from absolute alcohol or benzene–petroleum in colourless crystals, m. p. 119° (Found: C, 82·2; H, 5·2; S, 8·5. $C_{26}H_{20}OS$ requires C, 82·1; H, 5·3; S, 8·4%).

Alkaline hydrolysis. A solution of the sulphide (0·5 g.) in alcohol (50 c.c.) was treated with 10% sodium hydroxide solution (5 c.c.), boiled for 10 minutes, cooled, diluted with water, and kept in the ice-chest overnight. The precipitated solid crystallised from dilute alcohol in long colourless needles, m. p. 78—79° alone or mixed with phenyl benzhydryl sulphide (Finzi and Bellavita, *Gazzetta*, 1932, **62**, 699). Acidification of the mother-liquor produced the smell of thiophenol.

FOUAD I UNIVERSITY, CAIRO.

[*Received, June 6th*, 1941.]

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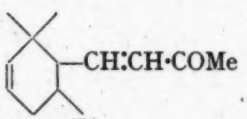
18. *Observations on the Absorption Spectra of Terpenoid Compounds. Part II. Irone.*

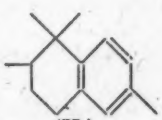
By A. E. GILLAM and T. F. WEST.

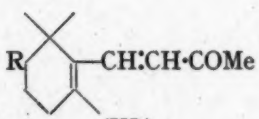
The absorption spectrum of irone is recorded and it is pointed out that the nature of the curve definitely precludes the presence of a conjugated dienone system such as is present in β-ionone (cf. Kilby and Kipping, J., 1939, 435). On the other hand, the absorption data indicate the presence of a monosubstituted αβ-unsaturated ketone group and are consistent with the presence of the R·CH:CH·CR:O structure similar to that found in α-ionone. The absorption spectra of two irone samples from different sources are sufficiently different to indicate that the natural ketone is a mixture. A critical examination of the crude thiosemicarbazones derived from these two samples supports this view (cf. also Ruzicka and co-workers, *Helv. Chim. Acta*, 1933, **16**, 1143; 1940, **23**, 935, 959; Tiemann and Krueger, *Ber.*, 1893, **26**, 2675; 1895, **28**, 1757).

ON the basis of analytical results and the examination of oxidation products Tiemann and Krueger (*locc. cit.*) assigned the structure (I) to the naturally occurring ketone *d*-irone, but the synthesis of a ketone possessing this formula claimed by Merling and his co-workers (*Annalen*, 1909, **366**, 119) has recently been disproved (Ruzicka, Seidel, and Schinz, *Helv. Chim. Acta*, 1933, **16**, 1143; 1940, **23**, 935), although Verley's synthesis (*Bull. Soc. chim.*, 1935, **2**, 1205) has apparently not been questioned. Ruzicka and his collaborators (1933, *loc. cit.*) concluded that irone has in fact the empirical formula $C_{14}H_{22}O$, and the structure (II) then advanced for its dehydration product, irene, was subsequently confirmed synthetically by Bogert and Apfelbaum (*J. Amer. Chem. Soc.*, 1938, **60**, 930). The structural formula of irone, however, remains obscure. For instance, Ruzicka *et al.* (1933, *loc. cit.*) concluded that the new formulation for irene corresponded to the structure (III; R = Me) for the ketone, but the production of ββγ-trimethylpimelic acid by ozonolysis was difficult to reconcile with this, and they suggested the possibility of (IV), with (III; R = Me) as an intermediate produced by pinacolin rearrangement of (IV) during the formation of irene.

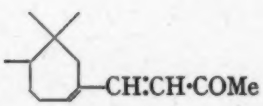


(I.)


(II.)



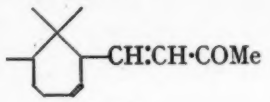
(III.)



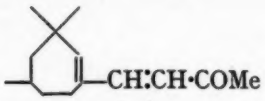
(IV.)

More recently Ruzicka, Schinz, and Seidel (*locc. cit.*, 1940) have stated that irone is undoubtedly a mixture of isomeric ketones, and (III; R = Me) and (VII) may exist together with (IV) or (V) in the natural ketone, the last two explaining the formation of ββγ-trimethylpimelic acid. Stoll and Scherrer (*Helv. Chim. Acta*, 1940, **23**, 941) reported that the properties of the synthetic ketone (VI) showed that " la présence d'un cycle heptanique ne suffit nullement à elle seule à produire l'odeur typique de l'irone," and Ruzicka and Schinz (*Helv. Chim. Acta*, 1940, **23**, 959) found that a synthetic ketone which was

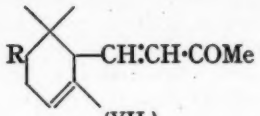
either 6-methyl-α-ionone (VII; R = Me) or 6-methyl-β-ionone (III; R = Me) did not simulate the properties of irone.



(V.)



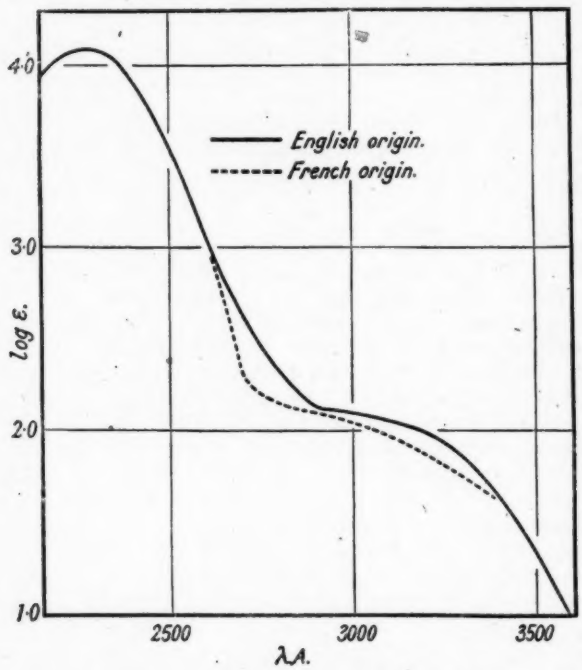
(VI.)



(VII.)

(VIII.) CMe_2:CH·$[CH_2]_2$·CMe:CH·CH:CH·COMe

Since the absorption spectrum of a compound affords such a definite means of deciding between an αβ-unsaturated ketone and a dienone, it was decided to examine that of a sample of natural irone with a view to eliminate some of the postulated formulæ. Accordingly, a specimen of oil of orris obtained from a French source was purified by vacuum distillation, and the irone isolated through the compound with *p*-phenylhydrazinesulphonic acid, and when it was certain that the ketone had the required analytical constants, its absorption spectrum was determined. The results are shown in the figure and Table I. The first point that emerges is that the absorption curve is perfectly characteristic of an αβ-unsaturated ketone and this fact alone is sufficient to disprove the presence of a dienone structure, since we know that typical compounds of this type absorb at much longer wave-lengths [cf. β-ionone (III; R = H) and ψ-ionone (VIII) (Table I)].



Absorption spectrum of irone in ethyl alcohol.

From the observed absorption spectrum of irone, we can not only conclude that the active chromophoric group is C:C·C:O and not C:C·C:C·C:O, but using Woodward's generalisation (*J. Amer. Chem. Soc.*, 1941, **63**, 1123), we can infer that only one of the three hydrogen atoms capable of being attached to the ethylene linkage is replaced by other groups, *i.e.*, that the chromophore is either CHR:CH·CR:O or CH_2:CR·CR:O. Evans and Gillam (J., 1941, 815) have shown that α-substituted αβ-unsaturated ketones exhibit an absorption maximum situated at shorter wave-lengths than in the case of the corresponding β-substituted compounds. Hence, irone must be a β-substituted, αβ-unsaturated ketone. If any further evidence were needed, we have the fact that the short-wave absorption band of α-ionone (VII; R = H) is located at the same wave-length as that of irone (Burawoy, J., 1941, 20; Evans and Gillam, *loc. cit.*) and α-ionone is accepted as being a β-substituted, αβ-unsaturated ketone having what must be a closely similar structure to that of irone.

TABLE I.

Compound.	*K*-Band.† $\lambda_{max.}$	$\epsilon_{max.}$	*R*-Band.† $\lambda_{max.}$	$\epsilon_{max.}$
Irone (French)	2280	12,200	near 3080	108
Irone (English)	2280	12,500	near 3050	117
α-Ionone	2285 *	14,300	?	—
β-Ionone	2935 *	8,700	none	—
ψ-Ionone	2910 *	21,800	none	—

* Burawoy, J., 1941, 20.

† See Burawoy, J., 1939, 1177.

In order to obviate the possibility of erroneous inferences based on the examination of a single specimen, we obtained a second sample of irone from a different source (English orris oil). Its constants and purity were carefully checked, and the absorption spectrum examined. This specimen exhibited the same type of absorption spectrum as the first, with the short-wave band situated at identically the same wave-length (2280 A.), thus confirming the previous finding. The curves are shown in the figure,

but it will be noticed that, although both show a maximum at 2280 A., the general shape of the long-wave part of the curve differs in the two cases. Since these curves are each the mean of two independent determinations, we believe the slight differences to be real and that they are consistent with the specimens being mixtures of somewhat variable composition.

Ruzicka, Seidel, and Schinz (1933, *loc. cit.*) found m. p. 175° for the *p*-bromophenylhydrazone prepared from irone of German origin, whereas the thiosemicarbazone melted to a turbid liquid at 110—120° and became clear and free from bubbles at 130°. They confirmed the m. p. of 181° recorded by Chuit for the irone thiosemicarbazone prepared by him (*Rev. Gén. Chim.*, 1903, **6**, 433).

The sample of irone which we obtained from orris oil of French origin, yielded a *p*-bromophenylhydrazone, m. p. 174° (Gillam and West, *Nature*, 1941, **148**, 114), and a thiosemicarbazone which could be separated into two components: (*a*) m. p. 184—185°, and (*b*) melting turbid between 107—115° and becoming clear at 130°. The irone isolated from the orris oil distilled in England had similar constants and gave a *p*-bromophenylhydrazone, m. p. 175°, and two thiosemicarbazones, (*c*) m. p. 185°, and (*d*) m. p. 107—110°, clear at 131°. The nitrogen content of our thiosemicarbazones corresponded with those reported for equivalent derivatives by the authors mentioned, but the proportion of ketone yielding the higher-melting thiosemicarbazone was considerably higher in the oil of French origin. It may be significant that Ruzicka *et al.* (1933, 1940, *locc. cit.*) have stated that the ketone is undoubtedly a mixture of isomerides; the composition of which may depend on the province of origin of the orris root and the method of manufacturing the oil, but the nitrogen content of our pairs of thiosemicarbazones pointed strongly to the presence of ketones possessing different empirical formulæ (Table II). The absorption data for these compounds, which will be more conveniently considered in another communication, support this hypothesis. The yield of the characteristic *p*-bromophenylhydrazones was low, and it was unfortunately not possible to purify the residue obtained from the mother-liquors.

TABLE II.

Details of Irone Thiosemicarbazones.

Authors.	Source of oil.	M. p.	N, % (found).*
Chuit [1]	German	181°	15·85
Ruzicka, Seidel, and Schinz [2]	German	110—120°, clear at 130°	14·73
Gillam and West	French	(*a*) 184—185°	15·7
		(*b*) 107—115°, clear at 130°	14·5
Gillam and West	English	(*c*) 185°	15·2
		(*d*) 107—112°, clear at 131°	14·75

[1] *Loc. cit.* [2] *Loc. cit.*, 1933.

* Calc. for $C_{16}H_{27}N_3S$: N, 14·3%. Calc. for $C_{15}H_{25}N_3S$: N, 15·05%. Calc. for $C_{14}H_{23}N_3S$: N, 15·85%.

EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

(*a*) Commercial concrete oil of orris (112 g.) of French origin was distilled under reduced pressure, leaving a residue (95 g.), which was discarded, and suitable fractions redistilled. Two fractions, (i) (9 g.) having b. p. 108—120°/2 mm., α_D + 23·9°, $n_D^{19°}$ 1·4803, $d_{15}^{21°}$ 0·879, and (ii) (3·5 g.), b. p. 125—150°/2 mm., α_D + 13·7°, $n_D^{18°}$ 1·4700, $d_{15}^{21°}$ 0·885, were bulked and treated with *p*-phenylhydrazinesulphonic acid according to the method used by Schmidt (*Z. angew. Chem.*, 1900, **1**, 191; see also Ruzicka, Seidel, and Schinz, *Helv. Chim. Acta*, 1933, **16**, 1143) for the isolation of the ionones. After removal of the uncombined constituents (6·75 g.) by ten extractions with ether (Schmidt, *loc. cit.*), the aqueous solution was treated with phthalic anhydride, and the liberated ketone distilled in steam. The oil extracted from the distillate with ether was twice carefully distilled under reduced pressure, whereupon the main fraction (4·5 g.) had b. p. 106—108°/2 mm., α_D + 37·5°, $n_D^{17°}$ 1·5017, $d_{15}^{20°}$ 0·912 (Found: C, 81·2; H, 10·6. Calc. for $C_{13}H_{20}O$: C, 81·2; H, 10·4%. Calc. for $C_{14}H_{22}O$: C, 81·5; H, 10·7%).

The ketone (0·8 g.) yielded a *p*-bromophenylhydrazone which was recrystallised twice from methyl alcohol to give white crystals (0·1 g.), m. p. 174° (sintering at 165°) when rapidly heated (Found: N, 7·5. Calc. for $C_{20}H_{27}N_2Br$: N, 7·5%. Calc. for $C_{19}H_{25}N_2Br$: N, 7·75%).

Irone (2 g.) and thiosemicarbazide (1·4 g.) were treated as described by Ruzicka, Seidel, and Schinz (*Helv. Chim. Acta*, 1933, **16**, 1150). The crude thiosemicarbazone (2·05 g.) (which softened at 100°, lost shape at 108°, and finally became clear at 145°) was dissolved in warm methyl alcohol (15 ml.), and the solution kept at 0° overnight. The crystals (0·7 g.) which separated melted at 178°, and after twice recrystallising from methyl alcohol had m. p. 184—185° (Found: N, 15·7, 15·7%). Water (1 ml.) was added to the filtrate and an oil separated on standing. This oil was washed with dilute methyl alcohol, and after drying for two days in a vacuum desiccator, the product (1·1 g.) melted at 105° (sintering at 60°). This was dissolved in *cyclo*hexane–benzene (4 : 1) (charcoal) and the solution allowed to concentrate, and after a repetition of this process the

small blunt crystals obtained (0·2 g.) became turbid at 107°, ran to the bottom of the tube at 115°, and became clear and free from bubbles at 130° (Found: N, 14·5%).

(*b*) Concrete oil of orris (83 g.), prepared in England by steam-distillation from orris root, was distilled under reduced pressure, and the appropriate fraction treated as in (*a*) above. The irone (3·5 g.) regenerated from the compound with *p*-phenylhydrazinesulphonic acid and distilled had b. p. 116—118°/3 mm., α_D + 46·6°, $n_D^{21°}$ 1·5015, $d_{15°}^{26°}$ 0·915.

The ketone (0·5 g.) yielded a *p*-bromophenylhydrazone which, after recrystallising from methyl alcohol, was obtained as small white crystals (0·1 g.) having m. p. 175° (sintering at 161°) unchanged by further recrystallisation (Found: N, 7·5. Calc. for $C_{20}H_{27}N_2Br$: N, 7·5%).

Irone (1·5 g.), treated with thiosemicarbazide (1·05 g.) as in (*a*) above, gave a crude thiosemicarbazone (1·6 g.) which softened at 101°, lost shape at 107°, and became clear at 135°. This was dissolved in hot methyl alcohol (12 ml.) and after standing at 0° overnight the crystals which separated (0·2 g.) had m. p. 180° (sintering at 176°) which after recrystallisation from methyl alcohol was raised to 185°, unaltered on admixture with the higher-melting thiosemicarbazone from (*a*) above (Found: N, 15·2, 15·2%). After separation of the crystals, the methyl alcohol was allowed to evaporate at room temperature, and the product dried in a vacuum desiccator over paraffin wax. The solid (1·2 g.) softened at 57°, lost shape at 84°, and finally melted at 100°. After twice recrystallising from *cyclo*hexane–benzene, the white crystals (0·3 g.) began to melt at 107°, ran to the bottom of the tube at 112°, and became clear at 131° (Found: N, 14·9, 14·6%). When mixed with the corresponding product from (*a*) above, this thiosemicarbazone began to melt at 107° and became finally free from bubbles at 132°.

Determinations of absorption spectra were made on a Hilger E_3 quartz spectrograph in conjunction with a Spekker photometer, standard methods being used.

We thank Mr. Roger K. Allen for suggesting an investigation of orris oil, and one of us (T. F. W.) is indebted to the Directors of Messrs. Stafford Allen and Sons, Ltd., for facilities, and to Mr. J. B. S. Wilson for technical assistance.

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STAFFORD ALLEN AND SONS, LTD., LONDON, N. 1.

[*Received, December 2nd,* 1941.]

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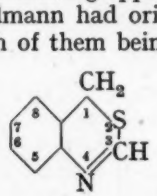
19. *Thiazinocyanines. Part I. Carbocyanines containing the 2 : 4-Benzthiazine Nucleus.*

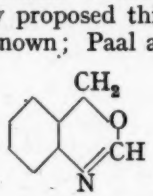
By BERNARD BEILENSON and FRANCES M. HAMER.

Cyanines containing a six-membered heterocyclic ring have been prepared for the first time. 3-Methyl-2 : 4-benzthiazine was condensed with quaternary salts containing a substituted β-aminovinyl group to give five new carbocyanine bases. Two of these were converted into their ethiodides, the carbocyanines themselves. Both 3-amino-2 : 4-benzthiazine ethiodide and also the base were condensed with a salt containing a substituted β-aminovinyl group, to give a γ-azatrimethincyanine and its base, respectively. Absorption maxima of the various dyes have been compared. The effect of replacing the benzthiazole by the 2 : 4-benzthiazine nucleus in carbocyanines is to produce a hypsochromic shift.

THE nomenclature adopted in this paper for the parent base, 2 : 4-benzthiazine (I), follows that of Richter's "Lexikon." Once the positions of the sulphur and the nitrogen atom in the ring are thus defined by the numbers, there can be no ambiguity as to that of the methylene group. The above name is therefore preferred to the 2 : 4 : 1-benzothiazine of *Chemical Abstracts* (*Decennial Index* for 1917—1926).

The following record of the nomenclature which has been used in the literature may be useful. Paal and Bodewig applied the name "Cumazon" to the 2 : 4-benzoxazine (II) (*Ber.*, 1892, **25**, 2961), although Widmann had originally proposed this name for its dimethyl derivative (III) (*Ber.*, 1883, **16**, 2576), both of them being unknown; Paal and Vanvolxem called (I) "Cumothiazon" (*Ber.*, 1894, **27**, 2413).


(I.)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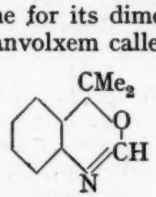
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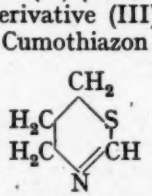
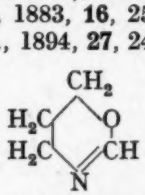
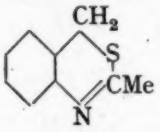

(IV.)

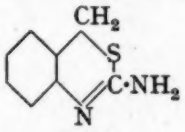

(V.)

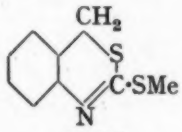
Gabriel and Posner, in pointing out the anomaly between Widmann's nomenclature and Paal's, suggested calling (I) and (II) "Phenpenthiazol" and "Phenpentoxazol," respectively (*Ber.*, 1894, **27**, 3509).

These terms are connected with those of "Penthiazolin" for (IV) (Gabriel and Lauer, *Ber.*, 1890, **23**, 87) and "Pentoxazolin" for (V) (Gabriel and Elfeldt, *Ber.*, 1891, **24**, 3213).

Our object was to introduce the 2 : 4-benzthiazine nucleus into cyanine dyes. Possible intermediates were 3-methyl-2 : 4-benzthiazine (VI) (Gabriel and Posner, *Ber.*, 1894, **27**, 3509), 3-amino-2 : 4-benzthiazine (VII) (*idem*, *ibid.*, 1895, **28**, 1029), and 3-methylthio-2 : 4-benzthiazine (VIII) (Paal and Commerell, *Ber.*, 1894, **27**, 2427), which we hoped would give reactive quaternary salts.

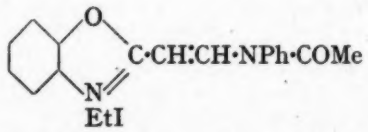

(VI.)

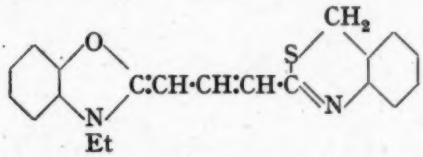

(VII.)


(VIII.)

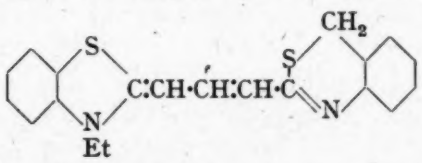
Anthranilic acid, which is the starting point in the synthesis of (VI), was reduced electrolytically to *o*-aminobenzyl alcohol (Mettler, *Ber.*, 1905, **38**, 1745); by a modification of Gabriel and Posner's method, this was converted into *o*-aminobenzyl chloride hydrochloride, which was condensed with thioacetamide, according to their method (*loc. cit.*), to give (VI). Attempts to prepare the methiodide and metho-*p*-toluenesulphonate gave unattractive products which could not be condensed with ethyl orthoformate in the presence of pyridine. Since quaternary salts of (VI) would have the structure with which Mills and Smith found reactivity of the methyl group to be correlated (J., 1922, **121**, 2724), we conclude that we were unsuccessful in obtaining the desired quaternary salts. However, having failed here, we developed the following line of attack through the base (VI) itself.

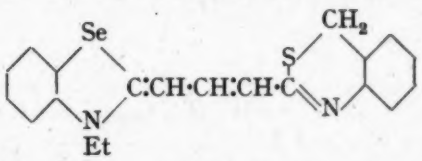
Unsymmetrical carbocyanines were prepared by I.C.I. Ltd., Piggott and Rodd by condensing two quaternary, heterocyclic ammonium salts, one containing a reactive methyl, the other a reactive sub-

(IX.) 


(X.)

stituted β-aminovinyl group (B.P. 454,898/1930), which latter intermediates, *e.g.* (IX), they had described (B.P. 344,409/1929). Kendall found that a quinoline base, containing a reactive methyl group, could be condensed with a salt containing a substituted β-aminovinyl group (B.P. 456,362/1935), resulting in a base, the quaternary salt of which would be a carbocyanine. Preparative details were given by Barent and Kendall (B.P. 477,483/1936), and two such carbocyanine bases were described. We have now prepared five carbocyanine bases of a new type, by condensing 3-methyl-2 : 4-benzthiazine (VI) with intermediates containing a substituted β-aminovinyl group. Thus (VI) and (IX) gave the trimethincyanine base (X); bases (XI) and (XII) containing the benzthiazole and benzselenazole in

(XI.) 

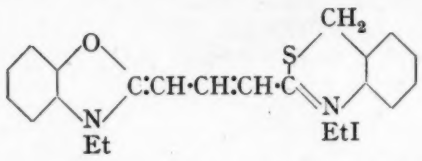

(XII.)

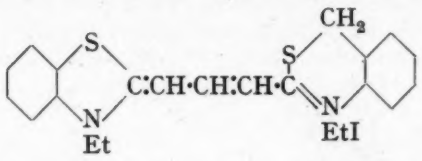
place of the benzoxazole nucleus were also prepared, besides one containing a 6 : 7-benzbenzoxazole and one a 4 : 5-benzbenzthiazole nucleus.

Absorption spectra of methyl-alcoholic solutions of the dyes were obtained by use of a wedge spectrograph. When the benzoxazole nucleus is replaced by the benzthiazole and the benzselenazole nucleus, respectively, the maximum shifts 200 A. towards the region of longer wave-length. The introduction of a benz-group causes, in the two instances, shifts of 250 and 150 A. With all five bases, addition of sulphuric acid to the methyl-alcoholic solution has a bathochromic effect, the shifts of maximum varying from 600—800 A. Thus the yellow solution of (X) becomes orange, the orange of (XI) becomes pink, and the red of its 4 : 5-benz-derivative becomes purple. The absorption curves of the bases are rounded, but those of the acid salts are narrower, with more sharply defined maxima. This group of substances comprises some powerful sensitisers for gelatino silver bromide emulsions.

Unsymmetrical carbocyanines (XIII) and (XIV) containing the 2 : 4-benzthiazine nucleus, were prepared by heating the bases (X) and (XI), respectively, with excess of ethyl *p*-toluenesulphonate,

followed by treatment with potassium iodide. These carbocyanines possess sharp absorption bands. Replacement of the benzoxazole by the benzthiazole nucleus, in passing from (XIII) to (XIV), causes

(XIII.) 



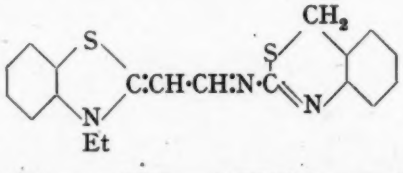
(XIV.)

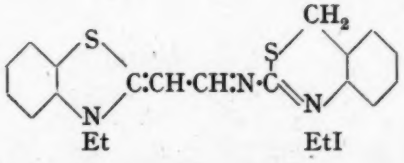
the usual bathochromic shift, its value being 300 A. It is particularly interesting to compare the unsymmetrical oxathiacarbocyanine (Beilenson, Fisher, and Hamer, *Proc. Roy. Soc.*, 1937, *A*, **163**, 138) with (XIII) and the symmetrical thiacarbocyanine (Fisher and Hamer, *ibid.*, 1936, *A*, **154**, 703) with (XIV): the effect of replacing the five-membered benzthiazole by the six-membered 2 : 4-benzthiazine nucleus, in these two instances, is to shift the absorption maximum 200 and 270 A., respectively, towards the blue. The absorption maxima of the new ethiodides (XIII) and (XIV) lie 550 and 650 A., respectively, nearer to the red than the absorption maxima of the corresponding bases; they approximate in position to those of acid solutions of the corresponding bases, lying, in each instance, 50 A. nearer to the blue. The ethiodides are good sensitisers, but, surprisingly, their action closely resembles that of the bases.

This abnormality in sensitising action might lie either with the ethiodide or with the base. It is attributed to the latter, for the reason that with the carbocyanines, (XIII) and (XIV), the shifts on passing from absorption maximum to sensitising maximum are 300 and 200 A., respectively, which may be regarded as normal (cf. Bloch and Hamer, *Phot. J.*, 1928, **68**, 21), whereas with the bases (X) and (XI) the corresponding shifts are exceptionally high, being 850 and 750 A., respectively. The sensitising action of the base is then what might be expected from an acid salt of the base. At first this seemed fully accounted for by the fact that the photographic emulsion used for the tests was on the acid side, p_H 6·5. On carrying them out, however, with a definitely alkaline emulsion, p_H 7·5, we found that the sensitising action of the base was unaltered.

In assigning chemical names to the cyanines described in this paper, systematic nomenclature is used. The bases are given the simplified names which were suggested by Dr. J. T. Hewitt, F.R.S., and have been applied to similar dye bases (Hamer, J., 1940, 799).

Two interesting dyes containing the chain :CH·CH:N·(or ·CH:CH·N:) have been synthesised. For this, 3-amino-2 : 4-benzthiazine (VII) was prepared from *o*-aminobenzyl chloride hydrochloride and thiocarbamide, by the method of Gabriel and Posner (*Ber.*, 1895, **28**, 1029). Although we could not make quaternary salts of 3-methyl-2 : 4-benzthiazine, we made 3-*amino*-2 : 4-*benzthiazine ethiodide*. Kendall has recorded the condensation in pyridine of 2-aminobenzthiazole and an intermediate containing a substituted β-aminovinyl group (B.P. 447,038/1934). By condensing 3-amino-2 : 4-benzthiazine with an intermediate of this type, we obtained the dye base (XV). Moreover, by condensing 3-amino-2 : 4-benzthiazine ethiodide with the same intermediate, we prepared the *azatrimethincyanine* (XVI), which is the ethiodide of (XV).

(XV.) 



(XVI.)

The substances (XV) and (XVI) bear a close structural relationship to (XI) and (XIV), respectively, the one difference being that the nuclei in (XV) and (XVI) are linked by the chain :CH·CH:N·, instead of by :CH·CH:CH·. On passing from the trimethincyanine (XIV) to the azatrimethincyanine (XVI), the absorption maximum undergoes a hypsochromic shift of 900 A.; here it is interesting to note the rather smaller hypsochromic shift which Fisher and Hamer found on passing from certain trimethincyanines to αβ (or βγ)-diazatrimethincyanines and the much greater one on passing to an αγ-diazatrimethincyanine (J., 1937, 907). On passing from the trimethincyanine base (XI) to the azatrimethincyanine base (XV), the small shift, 50 A., is bathochromic. The new base (XV) has a broad absorption band, and its ethiodide (XVI) a more sharply defined band. One difference between this base and the five trimethincyanine bases is that it shows no deepening of colour on addition of sulphuric acid. Another striking difference is that the absorption maximum, on passing from base (XV) to ethiodide (XVI), shifts 300 A. towards the region of shorter wave-length, whereas in the trimethincyanine series the shift

is in the opposite direction. The azatrimethincyanine sensitised a gelatino silver chloride emulsion, but the base did not sensitise it.

Experimental.

o-Aminobenzyl Alcohol.—Mettler's method of electrolytic reduction of anthranilic acid was applied, but whereas he started with 5 g. (*Ber.*, 1905, **38**, 1745), the present scale was much larger. Anthranilic acid (100 g.), partially dissolved in 15% sulphuric acid (2000 c.c.), was placed in a 4-l. beaker as cathode chamber. Inside that was the anode chamber, a porous pot containing 15% sulphuric acid. Both anode and cathode were pure lead strip, and 200 sq. cm. of cathode were immersed. Mettler kept the temperature below 30° by water-cooling, but here it was kept at 15—20° by cooling with ice. Mechanical stirring proved advantageous, as did a reduction time (12 hours at an amperage of 13·5) which was twice that calculated. The solution was made just alkaline with ammonia, instead of with ammonium carbonate, but filtration, saturation with ammonium sulphate, and extraction with ether (200 c.c. × 3) were as described by Mettler. Nine such batches gave 454 g., with an average yield of 56%, as against his 69%. After recrystallisation from benzene (50 c.c. for 30 g.), the yield dropped to 46% and the m. p. was 84°, as recorded by him.

o-Aminobenzyl Chloride Hydrochloride.—The scale was four times that of Gabriel and Posner (*Ber.*, 1894, **27**, 3509). The time of heating together crude *o*-aminobenzyl alcohol (20 g.; 1 mol.) and hydrochloric acid (*d* 1·195; 100 c.c.; 6 mols.), in a pressure bottle at 100°, was only 12 minutes, instead of 30. The hydrochloride was filtered off when cold, washed with ether, and dried at about 40°. The yield from eight such preparations was 84% (194 g.) as against their 76% yield (5·5 g.).

3-Methyl-2 : 4-benzthiazine (VI).—*o*-Aminobenzyl chloride hydrochloride (14 g.; 1 mol.) and thioacetamide (7 g.; 1·2 mols.) were ground together and heated on the water-bath for 15 minutes, and the mixture was made just alkaline with sodium hydroxide and steam-distilled, according to the method of Gabriel and Posner (*loc. cit.*). Whereas they on their smaller scale obtained a 78% yield (0·5 g.), the present yields of solid varied unaccountably from 19 to 63% (8 g.).

3-Amino-2 : 4-benzthiazine (VII).—*o*-Aminobenzyl chloride hydrochloride (20 g.) was ground with thiocarbamide (40 g.), and the mixture heated at 140° for 10 minutes and at 160—170° for 5 minutes, whereas Gabriel and Posner (*Ber.*, 1895, **28**, 1029) heated at 140—150° for 15 minutes. After alkali treatment, they by ether extraction obtained a 54% yield on their half scale. In the present preparation, after alkali treatment the solid was filtered off and purified by solution in dilute hydrochloric acid and reprecipitation with alkali, being thus obtained in 52% yield. After recrystallisation from spirit (2 c.c. per g.), the yield dropped to 40% and the m. p. was 135°, whereas Gabriel and Posner record 136—137° (Found after drying in a vacuum at 55—60° : N, 17·0. Calc. for $C_9H_8N_2S$: N, 17·1%).

3-Amino-2 : 4-benzthiazine Ethiodide.—3-Amino-2 : 4-benzthiazine (6·56 g.; 1 mol.) and ethyl iodide (9·6 c.c.; 3 mols.) were refluxed on the water-bath for 2 days. The gummy product, after being stirred with absolute alcohol (20 c.c.; 3·87 g. obtained), separated from absolute alcohol (40 c.c.) in 23% yield in cream-coloured crystals. It was dried to constant weight in a vacuum at 60—80° and analysed by the method of Carius; these methods of drying and analysis were employed throughout this work, except where otherwise stated (Found : I, 39·6. $C_{10}H_{13}N_2IS$ requires I, 39·65%). M. p. 220° (decomp.).

Trimethin[2-(*3-ethyldihydrobenzoxazole*)][3-(2 : 4-*benzthiazine*)] (X).—2-β-Acetanilidovinylbenzoxazole ethiodide (IX) (4·34 g.; 1 mol.), 3-methyl-2 : 4-benzthiazine (VI) (1·63 g.; 1 mol.) and pyridine (10 c.c.) were refluxed for 5 minutes. The product was poured into a mixture of aqueous ammonia (20 c.c., *d* 0·880) and spirit (20 c.c.). More aqueous ammonia (40 c.c.), diluted with water (40 c.c.), was added. When cold, the aqueous layer was decanted from the dark oil, which was washed with water. On stirring with acetone (10 c.c.) it crystallised (1·46 g.). After recrystallisation from ethyl acetate (12 c.c.), the yield was 37% (1·22 g.) (Found : S, 9·4. $C_{20}H_{16}ON_2S$ requires S, 9·6%). M. p. 138°. It formed bright orange crystals with a purple reflex. Their methyl-alcoholic solution had a rounded absorption curve with maximum at 4450 A. With addition of sulphuric acid (5 g. per 100 c.c.) the absorption curve had two maxima, at 4800 and 5050. The *dye* is a strong sensitiser for the green with a maximum at 5300 A., but the sensitising action is almost uniform up to 5400, extending to 5800 for moderate exposures.

Trimethin[2-(*3-ethyldihydro-6 : 7-benzbenzoxazole*)][3-(2 : 4-*benzthiazine*)].—This was prepared in a similar manner from 2-β-acetanilidovinyl-6 : 7-benzbenzoxazole ethiodide (4·84 g.), 3-methyl-2 : 4-benzthiazine, and pyridine, followed by aqueous ammonia, spirit, and water. After decantation of the cold aqueous layer, the residual pasty mass solidified on treatment with acetone (1·04 g. obtained). It separated from ethyl acetate (30 c.c.) in 21% yield (0·80 g.) in brown crystals with a blue reflex (Found : S, 8·2. $C_{24}H_{20}ON_2S$ requires S, 8·3%). M. p. 163°. The absorption maximum was at 4700 A. With addition of sulphuric acid (5 g. per 100 c.c.), there were two maxima at 4850 and 5200. The broad sensitising band has its maximum at 5400 A. and sensitivity extends beyond 6000.

Trimethin[2-(*3-ethyldihydrobenzthiazole*)][3-(2 : 4-*benzthiazine*)] (XI).—This was prepared from 2-β-acetanilidovinylbenzthiazole ethiodide (4·5 g.), 3-methyl-2 : 4-benzthiazine, and pyridine, boiling being continued for 30 minutes. The oily precipitate, obtained by treatment with spirit and aqueous ammonia, hardened on cooling and was filtered off and washed with water. It was extracted three times with hot benzene (60 c.c. × 3);

on considerable concentration, the *base* crystallised (0·86 g.). The product from two such experiments was first boiled out with methyl alcohol (40 c.c.) and then boiled with enough to dissolve it (850 c.c.). It was only on great concentration (to 25 c.c.) that crystallisation occurred. The yield was 14% (0·98 g.) (Found: S, 18·1. $C_{20}H_{18}N_2S_2$ requires S, 18·3%). M. p. 199—200°. A pyridine or methyl-alcoholic solution of the dull red crystals showed a broad absorption band with maximum at 4650 A. On addition of sulphuric acid (5 g. per 100 c.c.) to the latter, the maximum shifted to 5400 and was a sharper peak. The *dye* confers strong and almost uniform extra-sensitising from 5000—5700 A., with a maximum at about 5400; the sensitising extends to 6200, but there is considerable depression of blue sensitivity.

Trimethin[2-(3-*ethyldihydro*-4 : 5-*benzbenzthiazole*)][3-(2 : 4-*benzthiazine*)].—2-β-Acetanilidovinyl-4 : 5-benzbenzthiazole ethiodide (5 g.), 3-methyl-2 : 4-benzthiazine, and pyridine were refluxed for 7 minutes, and the reaction mixture treated as in other instances. The viscous product was filtered off and ground with acetone. The dark residue (2·8 g.) was boiled out with benzene (40 c.c.) and there crystallised a 23% yield (0·94 g.) of maroon-coloured needles, with a blue reflex (Found: S, 16·0. $C_{24}H_{20}N_2S_2$ requires S, 16·0%). M. p. 196°. Their methyl-alcoholic solution, or pyridine solution, had a broad indefinite absorption band, with its principal maximum at about 4800 A. On addition of sulphuric acid (5 g. per 100 c.c.), the band became well defined and had its maximum at 5500. The base gives weak sensitising, with a flat maximum at about 5800, but it also causes general desensitisation and fog.

Trimethin[2-(3-*ethyldihydrobenzselenazole*)][3-(2 : 4-*benzthiazine*)] (XII).—2-β-Acetanilidovinylbenzselenazole ethiodide (4·97 g.), 3-methyl-2 : 4-benzthiazine, and pyridine were heated together for 5 minutes, and the reaction mixture treated as before. When cold, the precipitate was ground with water (3·59 g. obtained). It was boiled out three times with benzene (20 c.c. × 3). The benzene extracts gave a 22% yield (0·86 g.) of dull orange crystals (Found: N, 7·2. $C_{20}H_{18}N_2SSe$ requires N, 7·05%). M. p. 212°, with previous shrinking. The absorption maximum was at 4650 A. in methyl alcohol or pyridine and shifted to 5450 on addition of sulphuric acid (5 g. per 100 c.c.) to the methyl alcohol. Although the substance depresses the blue sensitivity of a photographic emulsion, it is a fairly good sensitiser, with a maximum at 5200 A., and sensitisation extends to 6400.

[2-(3-*Ethylbenzoxazole*)][3-(4-*ethyl*-2 : 4-*benzthiazine*)]*trimethincyanine Iodide* (XIII).—Trimethin[2-(3-ethyldihydrobenzoxazole)][3-(2 : 4-benzthiazine)] (X) (1·63 g.; 1 mol.) and ethyl *p*-toluenesulphonate (4 g.; 4 mols.) were heated together at 150—155° for 1 hour. The melt was dissolved in hot spirit (12 c.c.) and treated with a hot solution of potassium iodide (5 g.) in water (7 c.c.). The water-washed product (2·26 g.) was recrystallised from methyl alcohol (30 c.c.) and thus obtained in 57% yield (1·39 g.) (Found: I, 26·0. $C_{22}H_{23}ON_2IS$ requires I, 25·9%). M. p. 237° (decomp.). It crystallised in red needles with a blue reflex. Absorption maxima were at 4700 and 5000 A. It is a good sensitiser, with its maximum action at 5300; sensitivity extends to 5700 for moderate exposures.

[2-(3-*Ethylbenzthiazole*)][3-(4-*ethyl*-2 : 4-*benzthiazine*)]*trimethincyanine Iodide* (XIV).—Trimethin[2-(3-ethyldihydrobenzthiazole)][3-(2 : 4-benzthiazine)] (XI) (0·7 g.; 1 mol.) and ethyl *p*-toluenesulphonate (0·8 g.; 2 mols.) were heated together at 150° for 1 hour. The viscous product was dissolved in hot spirit and treated with a hot aqueous solution of potassium iodide. The water-washed, crystalline solid (0·98 g.) was recrystallised from methyl alcohol (33 c.c.) and thus obtained in 61% yield (0·61 g.) (Found: I, 25·2. $C_{22}H_{23}N_2IS_2$ requires I, 25·1%). The dark bluish-grey needles had m. p. 231—232° (decomp.). The absorption maximum was at 5300 A. The broad sensitising band extended to 6400 and had its maximum at 5500 with a slight maximum at 4700.

γ-Azatrimethin[2-(3-*ethyldihydrobenzthiazole*)][3-(2 : 4-*benzthiazine*)] (XV).—2-β-Acetanilidovinylbenzthiazole ethiodide (4·5 g.; 1 mol.), 3-amino-2 : 4-benzthiazine (1·64 g.; 1 mol.), and pyridine (10 c.c.) were refluxed for 5 minutes. The hot reaction mixture was poured into aqueous ammonia (20 c.c., *d* 0·880) and spirit (20 c.c.), and further diluted with water (40 c.c.). The water-washed product (1·02 g.) was boiled out with benzene (25 c.c.), from which, on addition of light petroleum (b. p. 40—60°), it crystallised in 20% yield (0·71 g.) (Found: S, 18·1. $C_{19}H_{17}N_3S_2$ requires S, 18·25%). The brick-red crystals had m. p. 145° (decomp.). The broad absorption band had an indefinite maximum at 4700 A. The substance did not sensitise.

[2-(3-*Ethylbenzthiazole*)][3-(4-*ethyl*-2 : 4-*benzthiazine*)]-*γ-azatrimethincyanine Iodide* (XVI).—2-β-Acetanilidovinylbenzthiazole ethiodide (2·0 g.; 1 mol.), 3-amino-2 : 4-benzthiazine ethiodide (1·5 g.; 1 mol.), anhydrous potassium carbonate (180-mesh; 0·63 g.; 1 mol.), and absolute alcohol (10 c.c.) were stirred and heated together on the water-bath for 7 minutes. The product obtained on cooling (2·2 g.) was recrystallised from methyl alcohol (70 c.c.); yield, 74% (1·42 g.) (Found: I, 25·0. $C_{21}H_{22}N_3IS_2$ requires I, 25·0%). The dark yellowish product had m. p. 240° (decomp.). The absorption maximum was at 4400 A. The substance sensitised a gelatino chloride photographic emulsion from 4200 to 5000 A., with a maximum at 4700.

We are indebted to Dr. E. P. Davey for testing the sensitising action of the compounds and to Mr. E. D. Rowell for photographing the absorption spectra.

KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX. [*Received, November 3rd*, 1941.]

20. *A Chemotherapeutic Comparison of the Trypanocidal Action of Some Aromatic Diamidines.*

By J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. H. Self.

A study has been made of the relationship between chemical constitution and trypanocidal activity of a number of aromatic amidines. The greatest activity was shown by compounds of the type $NH_2 \cdot C(:NH) \cdot C_6H_4 \cdot X \cdot C_6H_4 \cdot C(:NH) \cdot NH_2$, in which X is a simple aliphatic chain in which one or more of the CH_2 groups are replaced by oxygen, or is an ethylenic linkage as in the stilbenes. The preparation of diamidino-compounds from the corresponding nitriles is discussed, and the synthesis of a number of such compounds and of the required nitriles described.

The direct trypanocidal action of synthalin {decamethylenediguanidine dihydrochloride, $NH_2 \cdot C(:NH) \cdot NH \cdot [CH_2]_{10} \cdot NH \cdot C(:NH) \cdot NH_2, 2HCl$} was first demonstrated by Lourie and Yorke (*Ann. Trop. Med. Parasit.*, 1937, **31**, 435), following the observations of Jancsó and Jancsó (*Z. Immunitätsforsch.*, 1935, **86**, 1) and of Artagaveytia-Allende (*ibid.*, 1936, **89**, 21) that this compound, when injected into mice infected with various pathogenic trypanosomes, exerted a curative action. This, however, they attributed to its hypoglycæmic properties rather than to any direct action on the trypanosome. Later, King, Lourie, and Yorke (*Lancet*, 1937, **233**, 136) prepared and examined a number of compounds, more or less closely related to synthalin, and found that symmetrical diamidinoalkanes showed an even greater trypanocidal action than that of the corresponding guanidine derivatives, the most active being 1 : 11-diamidinoundecane dihydrochloride, $NH_2 \cdot C(:NH) \cdot [CH_2]_{11} \cdot C(:NH) \cdot NH_2, 2HCl$.

This discovery of the trypanocidal action of the diamidino-compounds opened up a new field of investigation, and its extension to the aromatic compounds was undertaken by the present authors, in the hope that such compounds would more readily lend themselves to a study of the effects of substitution, and so to products of increased trypanocidal action and possible therapeutic application. To this end, a preliminary *in vivo* examination of the trypanocidal action of a number of such compounds was undertaken, and the present publication deals with their preparation and their comparative trypanocidal activity. The wider investigation of the more active of these compounds was undertaken by Prof. Yorke and his collaborators, in which it was shown that the most active trypanocidal compounds were the 4 : 4′-diamidino-derivatives of stilbene, of diphenoxypentane and of diphenoxypropane. These were also found to be active against leishmania and babesia infections. Against the latter 4 : 4′-diamidinodiphenyl ether was also found to be effective (Lourie and Yorke, *Ann. Trop. Med. Parasitol.*, 1939, **33**, 289; Warrington Yorke, *Trans. Roy. Soc. Trop. Med. Hygiene*, 1940, **33**, 463).

Clinical trials of certain of these compounds for the treatment of trypanosomiasis are in progress under the direction of the Therapeutic Trials Committee of the Medical Research Council. 4 : 4′-Diamidinostilbene and 4 : 4′-diamidinodiphenoxypentane have been successfully employed for the treatment of Mediterranean kala azar (Kirk and Sati, *Ann. Trop. Med. Parasitol.*, 1940, **34**, 82; Kirk and MacDonald, *ibid.*, 1940, **34**, 131) and of Indian kala azar (Adams and Yorke, *ibid.*, 1939, **33**, 323; 1940, **34**, 173). The more active compounds also give some promise of being useful in the treatment of babesia and other infections in cattle and domestic animals.

The starting point of the investigation was 4 : 4′-diamidinodiphenylmethane, $NH_2 \cdot C(:NH) \cdot C_6H_4 \cdot CH_2 \cdot C_6H_4 \cdot C(:NH) \cdot NH_2$, a symmetrical aromatic diamidine of approximately the same molecular complexity as 1 : 11-diamidinoundecane. As was expected, this compound exhibited definite *in vivo* trypanocidal activity, which was, however, of a lower order than that of the aliphatic diamidine. Many lines of development from this point suggested themselves and of these we mention the following : effect of nuclear substitution, of increasing the length of the hydrocarbon chain, of substituting hetero-atoms in the chain, of partly oxidised linkages, of unsaturated linkages, of substitution in the amidine groups, of the position of the amidine groups symmetrically or otherwise. It was obvious that all these lines could not be explored fully and, in seeking preliminary indications of these effects, we were naturally guided by considerations of accessibility of the compounds. Later, as methods were developed, it became possible to fill in some of the gaps in our schemes, and we drew certain inferences which enabled us to concentrate the work into fewer and more promising channels. Definite conclusions on any one point would only be justified on data from many more compounds than we have examined, but we give the deductions we have made, and the evidence on which they are based, in the following comparative tables, in which Am = $NH_2 \cdot C(:NH) \cdot$, R = $\cdot C_6H_4 \cdot$, M.T.D. = maximum tolerated dose (mice), M.E.D. = minimum effective dose, *i.e.*, the smallest dose which, when injected into infected mice, caused the complete disappearance of the try-

panosomes from the peripheral blood stream within 72 hours, M.C.D. = minimum curative dose, *i.e.*, the minimum single dose which caused the complete disappearance of the trypanosomes from the blood stream for a period of at least 28 days. The doses are in all cases given in mg./g. Ratio = M.T.D./M.C.D. Where the substituent amidine groups are other than 4 : 4′ in the aromatic nucleus, the position is given in parentheses. I = Intravenous, S = subcutaneous injection. These tables relate only to the effect on *T. equiperdum*, but the activity of some of these compounds on *T. rhodesiense* and *T. brucei* has also been examined and found to be of the same order.

TABLE I.

Homology of mononuclear diamidines.

Substance.		M.T.D.	M.E.D.	M.C.D.	Ratio.
Am·R·Am		—	No trypanocidal activity		—
Am·R·CH_2·Am	I	0·016	0·005	Not curative	—
Am·CH_2·R·CH_2·Am		—	No trypanocidal action		—

Products of this type show little or no activity.

TABLE II.

Homology in hydrocarbon chain linking binuclear amidines.

Am·R·R·Am	I	0·03	0·015	Not curative	—
Am·R·CH_2·R·Am	I	0·016	0·005	,,	—
Am·R·CHPh·R·Am		—	No trypanocidal action		—
Am·R·[CH_2]$_2$·R·Am	I	0·015	0·001	0·005	3
	S	0·07	0·001	0·005	14
Am·R·[CH_2]$_3$·R·Am	I	0·02	0·0025	0·01	2
	S	0·10	0·0025	0·02	5
Am·R·CH:CH·R·Am	I	0·025	0·005	0·01	2·5
	S	0·125	0·005	0·01	12·5
Am·R·CH:CH·CH:CH·R·Am	I	0·03	No trypanocidal action		—
	S	0·1	0·02	0·04	2·5

Maximum activity is shown by a chain containing two carbon atoms. The investigation of this series is being extended.

TABLE III.

Replacement of one CH_2 *group by another bivalent linkage.*

Am·R·CH_2·R·Am	I	0·016	0·005	Not curative	—
Am·R·O·R·Am	I	0·025	0·0075	0·0175	1·5
Am·R·S·R·Am	I	0·02	0·01	Not curative	—
Am·R·SO_2·R·Am		—	No trypanocidal action		—
Am·R·NH·R·Am	I	0·04	0·01	0·04	1
	S	0·08	0·005	0·02	4
Am·R·CH_2·CH_2·R·Am	I	0·015	0·001	0·005	3
	S	0·07	0·001	0·005	14
Am·R·CH_2·O·R·Am	I	0·015	0·0025	0·01	1·5
	S	0·07	0·0025	0·005	14
Am·R·CH_2·NH·R·Am	I	0·015	0·0025	Not curative	—
	S	0·01	0·0025	,,	—
Am·R·CH_2·CH_2·CH_2·R·Am	I	0·02	0·0025	0·01	2
	S	0·10	0·0025	0·02	5
Am·R·CH_2·CH_2·O·R·Am	I	0·015	0·0025	0·015	1
	S	0·08	0·0025	0·005	16
Am·R·CH_2·O·CH_2·R·Am	I	0·015	0·0005	0·0075	2
	S	0·10	0·001	0·01	10
Am·R·CH_2·S·CH_2·R·Am	I	0·02	0·01	Not curative	—
Am·R·CH_2·NH·CH_2·R·Am	I	0·025	No trypanocidal action		—
	S	0·06	0·04	Not curative	—

Replacement of CH_2 by O results in slightly enhanced activity, by NH in a diminution, and by S in a practical disappearance of activity.

TABLE IV.

Homology in chain containing one ether linkage.

Am·R·O·R·Am	I	0·025	0·0075	0·0175	1·5
Am·R·CH_2·O·R·Am	I	0·015	0·0025	0·01	1·5
	S	0·07	0·0025	0·005	14
Am·R·CH_2·CH_2·O·R·Am	I	0·015	0·0025	0·015	1
	S	0·08	0·0025	0·005	16
Am·R·CH_2·O·CH_2·R·Am	I	0·015	0·0005	0·0075	2
	S	0·10	0·001	0·01	10

Homology in this series has no marked effect on trypanocidal activity.

TABLE V.

Homology in chain containing two ether linkages.

Substance.		M.T.D.	M.E.D.	M.C.D.	Ratio.
Am·R·O·CH_2·O·R·Am	I	0·015	0·0025	Not curative	—
	S	0·08	0·0025	0·04	2
Am·R·O·[CH_2]$_2$·O·R·Am	I	0·03	0·0025	0·015	2
	S	0·07	0·0025	0·05	1·4
Am·R·O·[CH_2]$_3$·O·R·Am	I	0·04	0·0025	0·005	8
	S	0·08	0·0025	0·005	16
Am·R·O·[CH_2]$_4$·O·R·Am	I	0·025	0·004	Not curative	—
	S	0·04	0·01	0·02	2
Am·R·O·[CH_2]$_5$·O·R·Am	I	0·02	0·0012	0·0025	8
	S	0·1	0·0025	0·005	20
Am·R·O·[CH_2]$_6$·O·R·Am	I	0·017	0·0012	0·006	3
	S	0·1	0·0012	0·01	10
Am·R·O·[CH_2]$_7$·O·R·Am	I	0·007	0·0016	Not curative	—
	S	0·03	0·001	0·01	3
Am·R·O·[CH_2]$_{10}$·O·R·Am	I	0·02	0·005	Not curative	—
	S	0·1	0·005	0·075	1·3
Am·R·O·CH_2·R·CH_2·O·R·Am	I	0·08	0·06	Not curative	—
	S	0·1	No trypanocidal action		—
Am·R·CH_2·O·R·O·CH_2·R·Am	I	0·015	No trypanocidal action		—
	S	0·1	0·04	Not curative	—

Maximum activity appears with chains of 3 and 5 carbon atoms.

TABLE VI.

Replacement of one CH_2 *by* CH(OH) *or by* CO.

Am·R·CH_2·R·Am	I	0·016	0·005	Not curative	—
Am·R·CH(OH)·R·Am		—	No trypanocidal action		—
Am·R·CO·R·Am		—	,,	,,	—
Am·R·CH_2·CH_2·R·Am	I	0·015	0·001	0·005	3
	S	0·07	0·001	0·005	14
Am·R·CH_2·CO·R·Am	I	0·02	0·01	Not curative	—
	S	0·1	0·02	,,	—
Am·R·CH_2·NH·R·Am	I	0·015	0·0025	,,	—
	S	0·08	0·0025	,,	—
Am·R·CO·NH·R·Am		—	No trypanocidal action		—

Replacement of CH_2 by CH(OH) or by CO diminishes the activity.

TABLE VII.

Substitution in the amidine groups.

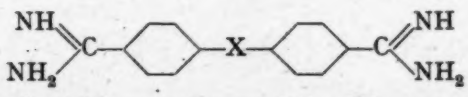
Am·R·R·Am	I	0·03	0·015	Not curative	—
*MeAm·R·R·AmMe	I	0·02	0·01	0·015	1·3
†Et_2Am·R·R·AmEt_2		—	No trypanocidal action		—
†PhAm·R·R·AmPh		—	,,	,,	—
Am·R·O·R·Am	I	0·025	0·0075	0·0175	1·5
*MeAm·R·O·R·AmMe	I	0·025	No trypanocidal action		—
Am·R·CH:CH·R·Am	I	0·025	0·005	0·01	2·5
	S	0·125	0·005	0·01	12·5
†NHPh·Am·R·CH:CH·R·Am·NHPh		—	No trypanocidal action		—

* In this formula MeAm indicates the structure NHMe·C(:NH). Formulæ marked † should be similarly interpreted.

Substitution in the amidine group is unfavourable to activity.

The last compound in Table XI is the only one of any noteworthy activity and this type of amidine is being examined further.

The general inference we draw from all data so far available is that the most active trypanocidal compounds are of the type



where X is a simple alkane chain in which one or more of the CH_2 groups are replaced by oxygen, or is an ethylenic linkage as in the stilbenes.

The method of preparation of the amidines included in the foregoing tables was essentially that of Pinner (" Die Imido Äther ") which involves the conversion of the nitriles into the imino-ethers and thence into the amidines. The best conditions for the two stages do not seem to have been discussed.

TABLE VIII.

Variation in the position of the amidine groups.

Substance.		M.T.D.	M.E.D.	M.C.D.	Ratio.
Am·R·CH_2·O·R·Am	I	0·015	0·0025	0·01	1·5
	S	0·07	0·0025	0·005	14
Am·R·CH_2·O·R·Am(3′)	I	0·03	0·0025	0·01	3
	S	0·1	0·0025	0·04	2·5
Am·R·CH:CH·R·Am	I	0·025	0·005	0·01	2·5
	S	0·125	0·005	0·01	12·5
Am·R·CH:CH·R·Am(3′)	I	0·015	0·005	0·01	1·5
	S	0·08	0·0025	0·04	2
Am·R·O·$[CH_2]_3$·O·R·Am	I	0·04	0·0025	0·005	8
	S	0·08	0·0025	0·005	16
Am(3)·R·O·$[CH_2]_3$·O·R·Am(3′)	I	0·03	0·0025	0·01	3
	S	0·1	0·0025	0·02	5
Am·R·O·$[CH_2]_5$·O·R·Am	I	0·02	0·00125	0·0025	8
	S	0·1	0·0025	0·005	20
Am(3)·R·O·$[CH_2]_5$·O·R·Am(3′)	I	0·025	0·0025	0·015	1·6
	S	0·08	0·005	0·01	8

3′ : 4-Diamidines appear to differ little from the corresponding 4 : 4′-compounds, but the 3 : 3′-compounds are definitely less active.

TABLE IX.

Monoamidines of similar structure to some active diamidines.

Am·R·O·R	—	No trypanocidal action	—
Am·CH_2·R·NH_2	—	,, ,,	—
Am·R·R·CN(2)	—	,, ,,	—
Am·R·CH:CHR	—	,, ,,	—
Am·R·CH:CH·R·NH_2(4)	—	,, ,,	—

Two amidine groups are needed for activity.

TABLE X.

Compounds in which one or both of the amidine groups are aliphatic in character.

Am·R·CH_2·O·CH_2·R·Am	I	0·015	0·0005	0·0075	2
	S	0·10	0·001	0·01	10
Am·CH_2·R·O·CH_2R·Am	I	0·01	0·0025	Not curative	—
	S	0·05	0·0025	0·05	1
Am·R·CH_2·CH_2·R·Am	I	0·015	0·001	0·005	3
	S	0·07	0·001	0·005	14
Am·CH_2·R·R·CH_2·Am	I	0·02	No trypanocidal action		—
	S	0·04	0·04	Not curative	—

Amidines in which the amidine group is aliphatic in character are markedly less active than those with the corresponding length of chain in which both amidine groups are aromatic.

TABLE XI.

Diamidines with miscellaneous linkages.

Am·R·N:N·R·Am	—	No trypanocidal action		—
Am·R·S·S·R·Am	—	,,	,,	—
Am·R·SO_2·NH·R·Am	—	,,	,,	—
Am·R·NH·CO·NH·R·Am	I 0·02	0·005	Not curative	—
	S 0·06	0·02	,,	—
Am·R·CH:CH·CO·R·Am	—	No trypanocidal action		—
Am·R·CH:CH·CH:CH·R·Am	I 0·03	,,	,,	—
	S 0·1	0·02	0·04	2·5
Am·R·O·CH_2·O·CH_2·O·R·Am	I 0·08	0·06	Not curative	—
	S 0·1	No trypanocidal action		—
Am·R·O·CH_2·CH_2·NH·R·Am	I 0·02	0·00125	0·01	2
	S 0·06	0·00125	0·01	6

Pinner states (*op. cit.*, p. 3) that the reaction R·CN + EtOH + HCl = R·C(NH)·OEt,HCl proceeds best with practically the theoretical quantities of the three reactants, but he is not quite consistent, since, for β-naphthimino-ether, he uses 1·7 molecules of alcohol and 1 molecule of hydrogen chloride (p. 72) and for *p*-toluimino-ether he uses 1 molecule of alcohol and saturates the solution with hydrogen chloride (p. 61). Earlier (p. 53—4) he says, in connection with benzimino-ether, that with 2 molecules of hydrogen chloride an unstable chloride of the type R·CCl(OR′)·NH_2,HCl is formed. This he regards as undesirable for various reasons and mentions that, on standing, it may decompose more or less completely into

ammonium chloride and esters. Pyman (J., 1930, 400) uses equimolecular quantities of alcohol and nitrile and saturates the solution with hydrogen chloride. H. King (private communication) uses 2 molecules of alcohol for each nitrile group and saturates with hydrogen chloride. In our experience with aromatic dinitriles 2 molecules of alcohol is the minimum quantity for a complete conversion into imino-ether hydrochloride, and we prefer to use 2·5—3 molecules. As most of the aromatic dinitriles are sparingly soluble in alcohol, we have used diluents in which the nitriles have some solubility, and of these chloroform, benzene, and nitrobenzene have proved useful. In certain cases a very considerable excess of alcohol served. King (J., 1939, 254) suggested the use of dioxan. The general procedure was to suspend the powdered nitriles in dry diluent with 2·5—3 molecules of absolute ethyl alcohol, saturate the liquid with hydrogen chloride at 0—5°, and keep it for 7—10 days at room temperature. The imino-ether hydrochlorides usually separated more or less completely, but in some cases it was found necessary to precipitate them by addition of light petroleum. Removal of the excess of hydrogen chloride (pump) as suggested by King was also a useful technique in some cases where the hygroscopic character of the crude imino-ether hydrochlorides rendered their isolation undesirable. No evidence was found for the existence of unstable chlorides such as were formulated by Pinner, but in the case of cyanophenyl cyanobenzyl ether the product approximated in composition to a trihydrochloride, the third molecule of hydrogen chloride possibly being associated with the ether oxygen atom.

The conversion of the imino-ether hydrochloride into amidine hydrochloride may not be as simple as is suggested by the equation

$$R{\cdot}C(OEt){:}NH,HCl + NH_3 = R{\cdot}C(NH_2){:}NH,HCl + EtOH$$

It seems to have been assumed that the reaction takes place between excess of ammonia and the imino-ether base liberated from its hydrochloride, but Knorr (*Ber.*, 1917, **50**, 229) claims to have demonstrated that it takes place between the free imino-ether and ammonium chloride and that the excess of ammonia plays no part in it. We have found, however, that benziminoether base, for example, does yield benzamidine base with alcoholic ammonia. In considering the optimum conditions for the conversion of the imino-ether hydrochlorides into the amidines the decomposition of imino-ether hydrochlorides by alcohol according to the equation

$$R{\cdot}C(OEt){:}NH,HCl + 2EtOH = NH_4Cl + R{\cdot}C(OEt)_3$$

(Reither and Hess, *Ber.*, 1907, **40**, 3020) must not be overlooked. In our experience it is necessary to use a large excess (10 molecules of ammonia per imino-ether group) of 10% absolute alcoholic ammonia to avoid the formation of traces of non-basic by-products (cf. acetamidine, *Org. Syntheses*, I—X, p. 5). It seems probable that the chief function of this excess is to displace the equilibrium

$$R{\cdot}C(OEt){:}NH,HCl + NH_3 \rightleftharpoons R{\cdot}C(OEt){:}NH + NH_4Cl$$

as far as possible in favour of ammonium chloride and imino-ether base, the latter being much more stable to alcohol than is the imino-ether hydrochloride.

The amidines generally presented no especial difficulties in isolation and purification, the hydrochloride being the salt most commonly used. In some cases the free base was more readily obtained and was therefore used in preliminary tests. Some of the hydrochlorides formed hydrates which could not be dehydrated without decomposition.

Few of the dinitriles required in these investigations have been described before and, indeed, the literature on the types in question is relatively scanty. We found early in this work that the Sandmeyer method was generally unsuitable for the preparation of any but relatively small quantities of dinitriles, so wherever possible we preferred the synthesis from two mononitriles. In the cases given in the table in the experimental section, however, we had to employ the Sandmeyer reaction, and we would call attention to the very simple but practical technique which we evolved for isolating these dinitriles, and which we describe in the experimental section. Of these nitriles a few require further comment.

4 : 4′-Dicyanobenzophenone was described by Brömme (*Ber.*, 1887, **20**, 521) as having been obtained by distillation of calcium 4-cyanobenzoate and having m. p. 204°, a method which, in our hands, gave traces only of this product. The Sandmeyer method on 4 : 4′-diaminobenzophenone gave a product, m. p. 162°, which was authentic 4 : 4′-*dicyanobenzophenone*, so the constitution of Brömme's product is obscure. The Sandmeyer reaction applied to 4 : 4′-diaminobenzhydrol yielded only traces of 4 : 4′-dicyanobenzophenone, but reduction of the latter with amalgamated aluminium gave the required 4 : 4′-*dicyanobenzhydrol*.

Since the completion of this work 4 : 4′-dicyanostilbene has been described by Lamb and White

(J., 1939, 1256), but the product obtained by them was probably impure. In our experience a purer product is obtained after vacuum sublimation of the crude reaction product.

3 : 4′-Diaminostilbene, required for 3 : 4′-*dicyanostilbene*, was obtained from the dinitro-compound by reduction with stannous chloride, which gave higher yields than the mixture of acetic and hydrochloric acids and zinc powder used by Harrison (J., 1926, 1236).

4-Nitrocinnamaldehyde (Fecht, *Ber.*, 1907, **40**, 2898), condensed with sodium 4-nitrophenylacetate in presence of acetic anhydride, gave 4 : 4′-*dinitro-αδ-diphenylbutadiene-α-carboxylic acid*, which was reduced to the corresponding diamine. The crude dinitrile obtained from this lost carbon dioxide during vacuum sublimation to yield 4 : 4′-*dicyano-αδ-diphenylbutadiene*.

4 : 4′-Diaminoazobenzene was readily obtained by reduction of the dinitro-compound with sodium sulphide. Previous methods described are reduction of 4-nitro-4′-aminoazobenzene (Noelting and Binder, *Ber.*, 1887, **20**, 3016) and hydrolysis of the mono- and di-acetamido-compounds (Wietzki, *Ber.*, 1884, **17**, 345; Minter, *Amer. Chem. J.*, 1883—1884, **5**, 283).

4 : 4′-Dicyano-αβ-diphenylethane has been isolated by Kattwinkel and Wolffenstein (*Ber.*, 1901, **34**, 2423; 1904, **37**, 3221) as a product of the oxidation of 4-toluonitrile by persulphates, but repetition of these experiments showed that the amounts formed were so small as to be impractical for the present purposes. Attempts to apply various methods, used for the preparation of diphenylethane or of 4 : 4′-dinitrodiphenylethane from benzyl chloride or 4-nitrobenzyl chloride, to 4-cyanobenzyl chloride, bromide, or iodide all failed. Diphenylethane itself can be obtained in excellent yields from benzyl chloride by the action of magnesium (Reichstein and Oppenauer, *Helv. Chim. Acta*, 1933, **16**, 1373), which is preferable to sodium (*J. Soc. Chem. Ind.*, 1936, 347T), as the latter reaction is less readily controlled and gives rise to by-products. The nitration of this to pure 4 : 4′-dinitrodiphenylethane is claimed (*J. Amer. Chem, Soc.*, 1930, **52**, 5040), but we were unable to obtain a pure product and resorted to the older method due to Roser (D.R.-P. 29,381; *Ber.*, 1887, **20**, 351, R) in which 4-nitrobenzyl chloride is reduced with alkaline stannite.

The yield of dinitrile obtained by the Sandmeyer reaction on 4 : 4′-diaminodiphenylethane was too small to be of practical utility. The 4 : 4′-dialdehyde has been prepared by Reichstein and Oppenauer (*loc. cit.*), and the complete series of reactions involved in the preparation of a nitrile from a hydrocarbon by this method is RH ⟶ R·CH_2Cl ⟶ R·CH_2·OAc ⟶ R·CH_2·OH ⟶ R·CHO ⟶ R·CH:NOH ⟶ R·CN. Although six stages are involved, the reactions are smooth except the first. The reagent used for the chloromethylation by Reichstein and Oppenauer is the solution obtained by saturating 40% formaldehyde with hydrogen chloride. This does largely consist of dichlorodimethyl ether, which is the active agent in the condensation, but it contains other substances which appear to polymerise and render the isolation of the pure chloromethyl compounds difficult. Better results were obtained by using pure dichlorodimethyl ether (Descude, *Centr.*, 1904, I, 1642). Since this work was done recent publications (*Compt. rend.*, 1939, **208**, 818; *Bull Soc. chim.*, 1939, **6**, 1025) on chloromethylation suggest an improved technique which should prove useful.

4 : 4′-*Dicyano-αγ-diphenylpropane* was prepared by the same series of reactions from the hydrocarbon. Attempts to reduce 4 : 4′-*dicyanobenzylideneacetophenone*, prepared by condensation of 4-cyanobenzaldehyde with 4-cyanoacetophenone, by hydrogen and palladium as applied to the unsubstituted substance (Straus and Grindal, *Annalen*, 1924, **439**, 279) failed.

Certain mononitriles, required for the synthesis of dinitriles with hetero-linkages, were prepared in considerable quantity. 4-Aminobenzonitrile has been prepared by reduction of the corresponding nitro-compound, but we preferred to convert 4-acetamidobenzaldehyde into the oxime, which on dehydration yielded 4-acetamidobenzonitrile, readily hydrolysed to the free amine by acid hydrolysis. 4-Hydroxybenzonitrile was prepared by the Sandmeyer method from 4-aminophenol, and 4-cyanobenzyl chloride by chlorination of 4-toluonitrile (Mellinghoff, *Ber.*, 1889, **22**, 3208).

4-Cyanobenzyl chloride with 4-hydroxybenzonitrile yielded 4-*cyanophenyl* 4-*cyanobenzyl ether* and with 3-hydroxybenzonitrile 3-*cyanophenyl* 4-*cyanobenzyl ether*. Similarly with 4-aminobenzonitrile 4 : 4′-*dicyanobenzylaniline* was obtained. Quinol and 2 molecules of 4-cyanobenzyl chloride gave 1 : 4-bis-(4′-cyanobenzyloxy)benzene, $C_6H_4(O{\cdot}CH_2{\cdot}C_6H_4{\cdot}CN)_2$. The 4 : 4′-dicyanodiphenoxyalkanes,

$$CN{\cdot}C_6H_4{\cdot}O{\cdot}[CH_2]_n{\cdot}O{\cdot}C_6H_4{\cdot}CN$$

were prepared by condensation of the appropriate αω-dibromoalkane with sodium 4-cyanophenoxide; *p*-xylylene dibromide yielded ωω′-bis-(4′-cyanophenoxy)-*p*-xylene, $C_6H_4(CH_2{\cdot}O{\cdot}C_6H_4{\cdot}CN)_2$. By use of an excess of the alkylene dibromide the ω-bromoalkoxybenzonitriles may be obtained (cf. *Org. Syntheses*, I—X, p. 425) and 4-cyano-β-phenoxyethyl bromide gave 4 : 4′-*dicyano-β-phenoxyethylaniline* on condensation with 4-aminobenzonitrile. The hydrolysis of 4-cyanobenzyl chloride has been carried out by Banse

(*Ber.*, 1894, **27**, 2170), who described a product, m. p. 134°, as 4-cyanobenzyl alcohol. It has now been shown that this is 4-carbamidobenzyl alcohol and the true *4-cyanobenzyl alcohol* has been obtained in excellent yield by a slight modification of Banse's procedure.

More drastic hydrolysis of 4-cyanobenzyl chloride with potassium hydroxide yields an acid, $C_{16}H_{14}O_5$, which Günther (*Ber.*, 1890, **23**, 1061) assumed, without much evidence, to be 4 : 4'-dicarboxydibenzyl ether. This acid has now been converted through the *acid chloride* and *amide* into the *dinitrile*, which was identical with the product obtained in small yields by condensing 4-cyanobenzyl alcohol with 4-cyanobenzyl chloride. Attempts to prepare this dinitrile from 4-cyanobenzyl alcohol by Meisenheimer's method (*Ber.*, 1908, **41**, 1421) for dibenzyl ether failed.

4-Cyanobenzaldehyde has been prepared by boiling 4-cyanobenzyl chloride with copper nitrate solution (Reinglass, *Ber.*, 1891, **24**, 2421; Moses, *Ber.*, 1900, **33**, 3624), but in our hands this method gave mixtures of alcohol, aldehyde, and acid. More recently (*J. Amer. Chem. Soc.*, 1936, **58**, 561) 2-cyanobenzaldehyde has been prepared from 2-cyanobenzylidene dibromide and silver nitrate in 50% yield only. We have found that nitrogen tetroxide in chloroform solution [an excellent method due to Cohen (J., 1897, **71**, 1050), which deserves to be more widely known] gives almost quantitative yields of the aldehyde from cyanobenzyl alcohol.

The considerable literature on the benzoin condensation did not suggest that an aldehyde such as 4-cyanobenzaldehyde would give the benzoin. The aldehyde reacted vigorously to give 4 : 4'-*dicyanodeoxybenzoin*. There does not appear to be any precedent for this in the literature, but it is well known that benzoins are readily converted into the deoxybenzoins by mild reducing agents, and it seemed possible that the benzoin might have been formed first and reduced rapidly by unconverted aldehyde. However, the yield of deoxybenzoin was practically the same after a few minutes as after 1 hour's boiling, a fact which would preclude that explanation. Some 4-cyanobenzoic acid was isolated, the amount being about half that required by the equation $3R{\cdot}CHO = R{\cdot}CO_2H + R{\cdot}CO{\cdot}CH_2R$.

4 : 4'-*Dicyanobenzanilide* was obtained in the usual way from *4-cyanobenzoyl chloride* and 4-aminobenzonitrile, and 4 : 4'-*dicyanobenzenesulphonanilide* similarly from 4-cyanobenzenesulphonyl chloride (Remsen, Hartman, and Muchenfuss, *Amer. Chem. J.*, 1896, **18**, 158).

The projected scheme for the preparation of 4-cyanophenyl 4-cyano-β-phenylethyl ether was to condense 4-nitro-β-phenylethyl bromide with 4-hydroxybenzonitrile to give 4-cyanophenyl 4-nitro-β-phenylethyl ether, which on reduction to the amino-compound, followed by a Sandmeyer reaction, should have given the required dicyano-ether. The condensation, however, gave traces only of the required ether and attempts to nitrate 4-cyanophenyl β-phenylethyl ether led to a dinitro-compound, probably 2-*nitro*-4-*cyanophenyl* 4-*nitro*-β-*phenylethyl ether*.

4-Nitro-β-phenylethyl bromide was smoothly reduced by hydrogen in presence of platinum oxide to 4-*amino*-β-*phenylethyl bromide*, which gave 4-*cyano*-β-*phenylethyl bromide* by the Sandmeyer method. The condensation of this with 4-hydroxybenzonitrile gave small yields of 4-*cyanophenyl* 4-*cyano*-β-*phenylethyl ether*.

Attempts to prepare 4 : 4'-dicyanodiphenylamine from 4-bromobenzonitrile and 4-aminobenzonitrile failed entirely and the following method was evolved. N-4-*Cyanophenylbenziminochloride*, prepared from 4-cyano-*N*-benzoylaniline, gave with sodium 4-cyanophenoxide N-4-*cyanophenylbenzimino*-4'-*cyanophenyl ether*, $CN{\cdot}C_6H_4{\cdot}N{:}CPh{\cdot}O{\cdot}C_6H_4{\cdot}CN$, which on rearrangement (cf. Chapman, J., 1925, **127**, 1992) yielded 4 : 4'-*dicyano*-N-*benzoyldiphenylamine*.

It was expected that removal of the benzoyl group would be effected during the preparation of the amidine *via* the imino-ether, but the amidine was in fact obtained with only small amounts of 4 : 4'-diamidinodiphenylamine, separated by means of its sparingly soluble *acid sulphate*. The amidine $NBz[C_6H_4{\cdot}C(:NH){\cdot}NH_2]_2$ decomposed smoothly at its melting point, giving excellent yields of 4 : 4'-*dicyanodiphenylamine* and benzamide, conveniently separated by sublimation. The sparing solubility of 4 : 4'-dicyano-*N*-benzoyldiphenylamine made the direct removal of the benzoyl group difficult, but sodium hydroxide in boiling ethylene glycol was a suitable hydrolytic agent for this substance.

Chemotherapeutic studies in the amidine series are being continued.

Experimental.

Amidines.—The general procedure has been outlined already and has been followed for the amidines for which the data have been summarised in the following table. In certain other cases the details are given. Two of the amidines included in the tables have been described : 1 : 4-diamidinobenzene ((Luckenbach, *Ber.*, 1884, **17**, 1436) and ωω'-diamidino-*p*-xylene (Glock, *Ber.*, 1888, **21**, 2660). The preparation of the compounds marked * has been described in detail in Brit. Pat. 507,565 and of that marked † in Brit. Pat. 510,097.

Compound.	Solvent.	Crystalline form.	M. p.	Formula.	Found, %.	Required.
4-Aminophenylacetamidine dihydrochloride	Alcohol	Plates	270°	$C_8H_{11}N_3,2HCl$	Cl, 31·7	32·0
4-Amidinomethylbenzamidine dihydrochloride	Methyl alcohol–acetone	Tetrahedra	280—285 (decomp.)	$C_9H_{13}N_3,2HCl$	Cl, 27·5	28·5
*4 : 4′-Diamidinodiphenyl dihydrochloride	Water	Slender needles	—	$C_{14}H_{14}N_4,2HCl$	N, 17·2 Cl, 22·6	18·0 22·8
4 : 4′-*Dimethylamidinodiphenyl dihydrochloride*	Alcohol–acetone	White prisms	—	$C_{16}H_{18}N_4,2HCl$	N, 16·9	16·5
4 : 4′-*Di-N-diethylamidinodiphenyl dihydrochloride*	Methyl alcohol–ether	Microcryst. powder	—	$C_{20}H_{26}N_4,2HCl$	N, 13·4	13·2
4 : 4′-*Di-N-phenylamidinodiphenyl dihydrochloride*	Water	Fine needles	—	$C_{26}H_{22}N_4,2HCl$	N, 11·8	12·1
*4 : 4′-Diamidinodiphenylmethane dihydrochloride	Alcohol–acetone	Slender prisms	—	$C_{15}H_{16}N_4,2HCl$	N, 15·6	15·5
4 : 4′-*Diamidinotriphenylmethane dihydrochloride*	,,	Microcryst. powder	—	$C_{21}H_{20}N_4,2HCl$	Cl, 18·1	17·7
4 : 4′-*Diamidinomethyldiphenyl dihydrochloride*	,,	Hexagonal plates	—	$C_{15}H_{18}N_4,2HCl$	N, 16·5	16·5
4-*Amidino-2′-cyanodiphenyl*	Water	Slender prisms	160—161	$C_{14}H_{11}N_3$	N, 18·4	19·0
*4 : 4′-Diamidinodiphenylethane dihydrochloride	5N-HCl	Small prisms	—	$C_{16}H_{18}N_4,2HCl,\frac{1}{2}H_2O$	N, 15·9 H_2O, 2·6	16·1 2·6
4 : 4′-*Diamidinodiphenylpropane dihydrochloride*	,,	Feathery needles	—	$C_{17}H_{20}N_4,2HCl$	N, 15·3	15·85
4 : 4′-*Diamidinobenzophenone dihydrochloride*	Methyl alcohol–ether		300	$C_{15}H_{14}ON_4,2HCl$	N, 15·9	16·4
4 : 4′-*Diamidinobenzhydrol dihydrochloride*	Methyl alcohol–ether	Microcrystalline	212	$C_{15}H_{16}ON_4,2HCl,3H_2O$	N, 14·0 Cl, 18·0	14·2 18·0
†4 : 4′-Diamidinostilbene dihydrochloride	Water	Needles	300	$C_{16}H_{16}N_4,2HCl,2H_2O$ $C_{16}H_{16}N_4,2HCl$ (dried at 100°)	N, 14·8 N, 16·4	15·0 16·6
4 : 4′-*Diamidinostilbene dimethanesulphonate*	,,	Long rods	—	$C_{16}H_{16}N_4,2CH_3{\cdot}SO_3H$	N, 12·3	12·3
3 : 4′-*Diamidinostilbene dihydrochloride*	Acetone–water	Clusters of prisms	300	$C_{16}H_{16}N_4,2HCl$	N, 16·2	16·6
4 : 4′-*Diamidino-αδ-diphenylbutadiene dihydrochloride*	Dil. HCl	Pale yellow prisms	—	$C_{16}H_{16}N_4,2HCl$	N, 14·9	15·4
4-*Amidinostilbene hydrochloride*	,,	Colourless plates	225—226	$C_{15}H_{14}N_2,HCl,H_2O$	N, 10·1	10·1
4-*Nitro-4′-amidinostilbene hydrochloride*	Acetic acid–HCl	Long yellow plates	300	$C_{15}H_{13}O_2N_3,HCl$	N, 13·9	13·8
4-*Amino-4′-amidinostilbene dihydrochloride*	,,	Plates	300	$C_{15}H_{15}N_3,2HCl$	N, 13·8	13·6
4 : 4′-*Diamidinobenzylideneacetophenone dihydrochloride*	Dil. HCl	Orange microcryst.	—	$C_{17}H_{16}ON_4,2HCl$	N, 15·5	15·3
4 : 4′-*Diamidinodeoxybenzoin dihydrochloride*	70% Alcohol	Small prisms	280—282	$C_{16}H_{16}ON_4,2HCl,1\frac{1}{2}H_2O$	N, 14·6 H_2O, 6·6	14·7 7·1
4-*Amidinodiphenyl ether*	Water	Hexagonal plates	126—127	$C_{19}H_{15}ON_3$	Equiv., 213	212
*4 : 4′-Diamidinodiphenyl ether	,,	Irregular plates	215—216	$C_{14}H_{14}ON_4$	N, 22·0	22·0
4 : 4′-Diamidinodiphenyl ether dihydrochloride	2N-HCl	Slender needles	—	$C_{14}H_{14}ON_4,2HCl,2H_2O$	N, 15·4 Cl, 19·4	15·4 19·55
*4 : 4′-*Diamidinodiphenyl sulphide*	Water	Spear-shaped plates	209—210 (decomp.)	$C_{14}H_{14}N_4S$	N, 20·2	20·7
4 : 4′-*Diamidinodiphenylsulphone dihydrochloride*	Methyl alcohol–ether	Colourless prisms	290 (decomp.)	$C_{14}H_{14}O_2N_4S,2HCl$	N, 14·9	14·9
*4-Amidinophenyl 4-amidinobenzyl ether	Water	Flat prisms	232—233	$C_{15}H_{16}ON_4$	N, 20·5	20·9
4-*Amidinophenyl 4-amidinobenzyl ether dihydrochloride*	Methyl alcohol–acetone	Heavy prisms	—	$C_{15}H_{16}ON_4,2HCl$	N, 16·3	16·4
3-*Amidinophenyl 4-amidinobenzyl ether dihydrochloride*	Alcohol	Slender prisms	—	$C_{15}H_{16}ON_4,2HCl,\frac{1}{2}H_2O$	N, 16·0 15·9	16·0 —
4-*Amidinomethylphenyl 4-amidinobenzyl ether*	Water	Diamond-shaped plates	182	$C_{16}H_{18}ON_4$	N, 19·6	19·9
*4 : 4′-Diamidinobenzylaniline dihydrochloride	Alcohol–acetone		296	$C_{15}H_{17}N_3,2HCl,H_2O$	N, 19·65 H_2O, 4·25	19·55 5·0
*4 : 4′-Diamidinodibenzylamine trihydrochloride	Conc. HCl	Prisms	—	$C_{16}H_{19}N_3,3HCl$	N, 17·8 Cl, 27·3	17·9 27·3
4 : 4′-*Diamidinodibenzyl ether*	Water	Pearly leaflets	195 (decomp.)	$C_{16}H_{18}ON_4$	N, 20·0	19·9
4 : 4′-*Diamidinodibenzyl ether dihydrochloride*	Aqueous alcohol–acetone	Long prisms	—	$C_{16}H_{18}ON_4,2HCl,H_2O$	N, 14·9 H_2O, 4·9	15·0 4·8
*4 : 4′-Diamidinodibenzyl sulphide	Aqueous alcohol	Colourless needles	198—199 (decomp.)	$C_{14}H_{12}N_4S$	N, 18·4	18·8
4-*Amidinophenyl 4-amidino-β-phenylethyl ether dihydrochloride*	Aqueous alcohol–acetone	Dense prisms	—	$C_{16}H_{16}ON_4,2HCl,H_2O$	N, 14·7	15·0
4 : 4′-*Diamidinodiphenoxymethane dihydrochloride*	Water	Colourless prisms	249 (decomp.)	$C_{13}H_{16}O_2N_4,2HCl$	N, 15·7	15·7
*4 : 4′-Diamidino-αβ-diphenoxyethane	,,	,, ,,	234—235 (decomp.)	$C_{14}H_{16}O_2N_4$	N, 18·9	18·9
4 : 4′-*Diamidino-αβ-diphenoxyethane dihydrochloride*	,,	Colourless needles	297	$C_{14}H_{16}O_2N_4,2HCl,H_2O$	N, 14·4 Cl, 18·4	14·4 18·3
*4 : 4′-Diamidino-αγ-diphenoxypropane dihydrochloride	Dil. HCl Alcohol	Fine needles Prisms	292 300	$C_{17}H_{20}O_2N_4,2HCl,H_2O$ $C_{17}H_{20}O_2N_4,2HCl$	N, 13·9 N, 14·2	13·9 14·5
3 : 3′-*Diamidino-αγ-diphenoxypropane dihydrochloride*	Alcohol–acetone	Fine needles	202—204 (decomp.)	$C_{17}H_{20}O_2N_4,2HCl$	N, 14·2	14·5
4 : 4′-*Diamidino-αδ-diphenoxybutane dihydrochloride*	Dil. HCl	Thin plates	259—261	$C_{18}H_{22}O_2N_4,2HCl,2H_2O$	N, 12·8 H_2O, 8·5	12·8 8·3
*4 : 4′-Diamidino-aε-diphenoxypentane	Water	Colourless plates	186 (decomp.)	$C_{19}H_{24}O_2N_4$	N, 16·5	16·5
4 : 4′-*Diamidino-aε-diphenoxypentane dihydrochloride*	Dil. HCl Alcohol	Fine needles Colourless prisms	233—234 (decomp.)	$C_{19}H_{24}O_2N_4,2HCl,2H_2O$	N, 12·5	12·5
4 : 4′-*Diamidino-aε-diphenoxypentane dimethanesulphonate*	90% Alcohol	Heavy prisms	—	$C_{19}H_{24}O_2N_4,2CH_3{\cdot}SO_3H$	N, 10·4	10·5
3 : 3′-*Diamidino-aε-diphenoxypentane dihydrochloride*	Dil. HCl	Matted needles	—	$C_{19}H_{24}O_2N_4,2HCl,2H_2O$	N, 12·3	12·5
4 : 4′-*Diamidino-aζ-diphenoxyhexane dihydrochloride*	,,	Prisms	246—247 (decomp.)	$C_{20}H_{26}O_2N_4,2HCl,2H_2O$	N, 12·1 H_2O, 7·6	12·1 7·8
4 : 4′-*Diamidino-aη-diphenoxyheptane*	Water	Colourless powder	175—177 (decomp.)	$C_{21}H_{28}O_2N_4$	N, 15·2	15·2
4 : 4′-*Diamidino-aη-diphenoxyheptane dihydrochloride*	Dil. HCl	Fibrous needles	245—246 (decomp.)	$C_{21}H_{28}O_2N_4,2HCl,2H_2O$	N, 11·6	11·7
*4 : 4′-Diamidino-aε-diphenoxydecane dihydrochloride	Alcohol–acetone Water	Rhombs Prisms	254	$C_{24}H_{34}O_2N_4,2HCl$	N, 11·4	11·6
ωω′-*Di-(4′-amidinophenoxy)xylene dihydrochloride*	,,	,,	—	$C_{32}H_{32}O_2N_4,2HCl,H_2O$	N, 12·0	12·0

Compound.	Solvent.	Crystalline form.	M. p.	Formula.	Found, %.	Required.
1 : 4-*Di*-(4′-*amidinobenzyloxy*)*benzene dihydrochloride*	Water	Slender prisms	—	$C_{21}H_{22}O_2N_4,2HCl,2H_2O$	N, 11·2	11·6
4 : 4′-*Diamidinodiphenoxydimethyl ether*	90% Alcohol		Indefinite	$C_{16}H_{18}O_2N_4$	N, 17·4	17·8
4 : 4′-*Diamidinodiphenoxydimethyl ether dihydrochloride*	Absolute alcohol–ether		—	$C_{16}H_{18}O_2N_4,2HCl$	N, 14·6	14·5
4 : 4′-*Diamidinoazobenzene dihydrochloride*	Dil. HCl	Red plates or rods	>300	$C_{14}H_{14}N_6,2HCl,H_2O$	N, 23·8	23·5
4 : 4′-*Diamidinodiphenyl disulphide dihydrochloride*	,,	Prisms	>300	$C_{14}H_{14}N_4S_2,2HCl,2H_2O$	N, 14·35	14·25
4 : 4′-*Diamidinobenzanilide*	Water	Microcryst.	245—250 (decomp.)	$C_{15}H_{15}ON_3$	N, 23·5	24·9
4 : 4′-*Diamidinobenzenesulphonanilide dihydrochloride*	Dil. HCl	Octohedra	239	$C_{13}H_{15}O_3N_3S,2HCl,4H_2O$	N, 15·3 Cl, 15·6	15·1 15·3
4 : 4′-*Diamidinodiphenylurea dimethanesulphonate*	Methyl alcohol	Prisms	—	$C_{13}H_{14}ON_6,2CH_3{\cdot}SO_3H,H_2O$	N, 16·6	16·6
*4 : 4′-Diamidino-β-phenoxyethylaniline	Water	,,	204 (decomp.)	$C_{16}H_{11}ON_3$	N, 24·0	24·0
*4 : 4′-Diamidino-β-phenoxyethylaniline dihydrochloride	Dil. HCl	,,	296—297	$C_{16}H_{11}ON_3,2HCl,2H_2O$	N, 17·8 Cl, 17·6	17·6 17·5
4 : 4′-*Diamidino-N-benzoyldiphenylamine*	Water	Colourless prisms	194 (decomp.)	$C_{21}H_{19}ON_3,2·5H_2O$	N, 17·0 H_2O, 10·4	17·4 11·2
4 : 4′-*Diamidinodiphenylamine sulphate*	Dil. H_2SO_4	Deep orange rhombs	—	$C_{14}H_{14}N_4,1·5H_2SO_4$	N, 17·7	17·5
4 : 4′-*Diamidinodiphenylamine dihydrochloride*	Alcohol		—	$C_{14}H_{14}N_4,2HCl,H_2O$	N, 20·2	20·3

The following dinitriles were prepared by methods given in the literature: Terephthalonitrile (*Annalen*, 1876, **180**, 89); 4-cyanophenylacetonitrile (*Ber.*, 1887, **20**, 3209); ωω′-dicyano-*p*-xylene (*Ber.*, 1888, **21**, 2659); 4 : 4′-dicyanodiphenyl (J., 1920, **117**, 1149); 2 : 4′-dicyanodiphenyl (*Ber.*, 1889, **22**, 3018); 4 : 4′-dicyanodiphenylmethane (*Ber.*, 1894, **27**, 2325); 4 : 4′-dicyanomethyldiphenyl (*Ber.*, 1933, **66**, 1475); 4 : 4′-dicyanodiphenyl disulphide (J., 1930, 1102); 4 : 4′-dicyanodibenzyl sulphide (*J. Amer. Chem. Soc.*, 1927, **49**, 2552); 4 : 4′-dicyanodiphenylurea (*ibid.*, 1921, **43**, 696); 4 : 4′-dicyanodibenzylamine (*Ber.*, 1900, **32**, 2629).

Dinitriles by the Sandmeyer Method.—The general procedure is that described in Organic Syntheses (Coll. Vol. I—IX, p. 500) with the difference that benzene is not used during the decomposition of the diazocyanide, and the cuprocyanide solution is maintained at temperatures varying with the diamine from 40° to 90° (there seems to be no general principle as to the optimum temperature for a given class of compound). The crude product, usually a dark, brittle, coke-like mass containing varying amounts of copper and weighing about the same as the original diamine employed, is dried and sublimed. The very simple technique employed is so marked an improvement on the conventional methods of extraction and repeated crystallisation as to merit some description.

The apparatus consists of a copper or gun-metal heating block approximately 70 × 60 × 60 mm., bored to take a 25 mm. test-tube and a thermometer. A short rod screwed into one side enables the block to be held in an ordinary boss and a retort stand at any desired angle. The sublimation is carried out in a 25 × 125 mm. Pyrex glass tube closed by a rubber stopper carrying a short length of 2 mm. bore glass tubing for connection to the vacuum pump; no cooling is needed. The tube is charged with the crude product (usually about 5 g.), followed by a loose asbestos plug. When the tube is inserted in the block, this plug should be a few mm. inside. The sublimations are carried out generally at 0·1—1 mm. pressure and at temperatures a little above or below the melting point. The nitriles usually form a hard crystalline crust in the tube a few mm. outside the block and are then almost invariably pure after one crystallisation. This process, used also for certain nitriles obtained by methods in which some amide may be formed, readily gives a sharp separation owing to the much greater volatility of the nitriles.

4 : 4′-*Dicyanotriphenylmethane*, m. p. 134—145°, was obtained in 5% yield from the diamine (Found: C, 85·4; H, 4·7; N, 9·35. $C_{21}H_{14}N_2$ requires C, 85·7; H, 4·8; N, 9·5%).

4 : 4′-*Dicyanobenzophenone*, obtained in 60% yield from the diamine, had m. p. 162° after crystallisation from acetic acid (Found: C, 77·9; H, 3·4; N, 12·05. $C_{15}H_8ON_2$ requires C, 77·6; H, 3·4; N, 12·05%). The *phenylhydrazone* formed yellow prisms from alcohol, m. p. 242—243° (Found: N, 17·2. $C_{21}H_{14}N_4$ requires N, 17·4%).

4 : 4′-*Dicyanobenzhydrol.*—4 : 4′-Dicyanobenzophenone (2 g.), suspended in ethyl alcohol (200 c.c.) containing ammonia, was treated with amalgamated aluminium foil (10 g.) under reflux, with occasional shaking, for 2 hours. The mixture was cooled, the liquid filtered, and the residue extracted with ethyl alcohol. The combined filtrate and extracts were evaporated to dryness, and the residue extracted with cold methyl alcohol (50 c.c.). The solution was again evaporated, and the residue crystallised from 50% acetic acid, yielding 0·65 g., m. p. 158—159° (Found: C, 76·9; H, 4·4; N, 12·0; *M*, Rast, 222. $C_{15}H_{10}ON_2$ requires C, 77·0; H, 4·3; N, 12·0%; *M*, 234).

4 : 4′-*Dicyanostilbene* (45% yield) crystallised from nitrobenzene in almost white prisms, m. p. 282° (Found: N, 12·1. $C_{16}H_{10}N_2$ requires N, 12·2%).

αβ-*Bis*-(4-*phenylbenzamidrazino*)*ethylene.*—The di-imino-ether obtained from 4 : 4′-dicyanostilbene (6 g.) was heated at 50° for 4 hours with a solution of phenylhydrazine (15 c.c.) in absolute alcohol (100 c.c.). The solid product obtained on cooling was washed with alcohol and acetone and boiled with water (4·5 l.). The solution was filtered, and hydrochloric acid (100 c.c., *d* 1·16) added to the filtrate. The product was recrystallised from water, the *dihydrochloride* (4 g.) separating in long cream-coloured needles, m. p. above 300° (Found:

N, 16·3; Cl, 13·3. $C_{28}H_{26}N_6,2HCl$ requires N, 16·2; Cl, 13·7%). The *base* crystallised from dilute acetone in clusters of brown needles, m. p. 261—262° (decomp.) (Found: N, 18·5. $C_{28}H_{26}N_6$ requires N, 18·8%).

3 : 4′-*Diaminostilbene*.—A mixture of 3 : 4′-dinitrostilbene (2·7 g.), stannous chloride (cryst., 17 g.), glacial acetic acid (10 c.c.), and hydrochloric acid (20 c.c., *d* 1·16) was heated to boiling. The stannichloride which separated on cooling was decomposed with sodium hydroxide, and the diamine crystallised from aqueous alcohol. Yield 1·2 g., m. p. 153°.

3 : 4′-*Dicyanostilbene* (yield, 26%) crystallised from glacial acetic acid in yellow needles, m. p. 137—138° (Found: N, 11·9. $C_{16}H_{10}N_2$ requires N, 12·2%).

4 : 4′-*Dinitro-αδ-diphenylbutadiene-α-carboxylic Acid*.—A mixture of sodium 4-nitrophenylacetate (38 g.) and 4-nitrocinnamaldehyde (30 g.), heated to 140—150°, was treated gradually with acetic anhydride (30 c.c.) and heated at 150° for 2 hours. Acetic anhydride (10 c.c.) was then added, and heating continued at 160° for a further 2 hours. The cold mixture was treated with water and left for 12 hours. The solid obtained after filtration was exhaustively extracted with boiling 0·5N-sodium carbonate, and the *acid* (24 g.) precipitated by boiling dilute hydrochloric acid. It crystallised from alcohol in squat yellowish-brown prisms, decomp. 295—300° (Found: N, 8·3. $C_{17}H_{12}O_6N_2$ requires N, 8·2%).

4 : 4′-*Dicyano-αδ-diphenylbutadiene*.—The dinitro-compound (10 g.) was heated with a solution of crystallised stannous chloride (50 g.) in hydrochloric acid (50 c.c., *d* 1·16) and glacial acetic acid (50 c.c.). After the vigorous reaction abated, the mixture was diluted, and tin removed as sulphide. Evaporation of the filtrate left the diaminocarboxylic acid dihydrochloride as a colourless solid (yield, 60%), which was tetrazotised without further purification. The crude product was sublimed at 250—260°/1—2 mm. The sublimate of 4 : 4′-*dicyano-αδ-diphenylbutadiene* crystallised from acetic acid in almost colourless, long plates or prisms, m. p. 260—261° (decomp.). Yield, 8% (Found: N, 10·85. $C_{18}H_{12}N_2$ requires N, 10·9%).

4-*Cyanostilbene*, obtained in 16% yield from 4-aminostilbene (Pfeiffer and Sergiewskaja, *Ber.*, 1911, **44**, 1110), crystallised from 80% acetic acid in fine needles, m. p. 114° (Found: N, 6·45. $C_{15}H_{11}N$ requires N, 6·8%).

4-*Nitro*-4′-*acetamidostilbene*.—A mixture of 4-nitrophenylacetic acid (45 g.), 4-acetamidobenzaldehyde (40 g.), and piperidine (12 c.c.) was heated under reflux at 160° for 6 hours. The cooled melt was ground with alcohol and washed thoroughly with alcohol and ether, the crude product (26 g.) being used in the next reaction. It crystallised from pyridine in yellow plates, m. p. 255° (Found: N, 10·3. $C_{16}H_{14}O_3N_2$ requires N, 9·9%).

4-*Nitro*-4′-*aminostilbene*.—The acetyl compound (10 g.) was refluxed with alcohol (100 c.c.) and hydrochloric acid (100 c.c., *d* 1·16) for 2 hours. When cool, the yellow hydrochloride was filtered off, and suspended in water, and the base (7·9 g.) liberated with sodium carbonate. It crystallised from pyridine in deep red plates, m. p. 245° (Strakosch, *Ber.*, 1873, **6**, 329, gives m. p. 229—230°).

4-*Nitro*-4′-*cyanostilbene* (yield, 31%) crystallised from glacial acetic acid in yellow needles, m. p. 247—249° (Found: N, 11·2. $C_{15}H_{10}O_2N_2$ requires N, 11·2%).

4-*Amino*-4′-*amidinostilbene*.—A hot solution of stannous chloride (6 g.) in hydrochloric acid (6 c.c., *d* 1·16) was added to a boiling solution of 4-nitro-4′-amidinostilbene hydrochloride (2 g.) in a mixture of glacial acetic acid (25 c.c.) and hydrochloric acid (10 c.c., *d* 1·16). The yellow stannichloride, which quickly separated, was cooled, collected, and dissolved in water. The free base was liberated by 50% sodium hydroxide solution (15 c.c.). The washed base was dissolved in cold glacial acetic acid and precipitated as the dihydrochloride by addition of concentrated hydrochloric acid (yield, 54%).

4 : 4′-*Diaminoazobenzene*.—A mixture of 4 : 4′-dinitroazobenzene (10 g.), crystallised sodium sulphide (100 g.), water (100 c.c.), and alcohol (300 c.c.) was refluxed for ½ hour. The hot liquid was filtered, and the diamine which separated was recrystallised from alcohol. Yield 3·2 g., m. p. 245—246°.

4 : 4′-*Dicyanoazobenzene* (yield, 45%) crystallised from glacial acetic acid in deep maroon needles, m. p. 270° (Found: N, 24·25. $C_{14}H_8N_4$ requires N, 24·1%).

4 : 4′-*Dicyanodiphenylethane*.—Diphenylethane-4 : 4′-dialdehyde (Reichstein and Oppenauer, *loc. cit.*) was converted into the oxime in the usual way, and this was boiled for 2 hours with 10 parts of acetic anhydride. Sufficient water was added to convert the acetic anhydride into acetic acid; the required dinitrile crystallised. Yield, 74%. The overall yield of dinitrile for the five stages from the dichloromethyl compound was 40%.

αγ-Diphenylpropane.—Dibenzyl ketone, b. p. 178—182°/10—11 mm., prepared by distillation of calcium phenylacetate in 500 g. lots in a steel retort, followed by fractionation of the distillate (yield, 60%), was reduced by the Clemmensen method to the hydrocarbon, b. p. 155—160°/9—10 mm. Yield, 70%. The higher-boiling fractions were returned to the next reduction. In this way 1 kg. of calcium salt gave 300 g. of pure αγ-diphenylpropane. The hydrocarbon was submitted to the same series of reactions as for αβ-diphenylethane. Chloromethylation gave a small yield of 4 : 4′-*dichloromethyl-αγ-diphenylpropane*, m. p. 103—106° (Found: Cl, 25·0. $C_{17}H_{18}Cl_2$ requires Cl, 24·2%). This was converted successively into 4 : 4′-*dihydroxymethyl-αγ-diphenylpropane*, m. p. 118—122° (Found: C, 79·4; H, 7·65. $C_{17}H_{20}O_2$ requires C, 79·6; H, 7·87%), the 4 : 4′-dialdehyde (oil), 4 : 4′-dialdoxime (m. p. 125—127°), and finally 4 : 4′-*dicyano-αγ-diphenylpropane*. This formed white prisms from alcohol, m. p. 94—95° (Found: N, 11·0. $C_{17}H_{14}N_2$ requires N, 11·4%). The overall yield from the dichloromethyl compound was 35%.

4 : 4′-*Dicyanobenzylideneacetophenone.*—4-Cyanobenzaldehyde (2·6 g.) and 4-cyanoacetophenone (2·9 g.) were boiled in absolute alcohol containing piperidine (0·2 g.) for 3 hours. The product which crystallised on cooling (2·6 g.; yield 60%) was recrystallised from glacial acetic acid, forming pale yellow, fibrous needles, m. p. 216—217° (Found : N, 11·0. $C_{17}H_{10}ON_2$ required N, 10·85%). Other condensing agents such as sodium hydroxide or sodium ethoxide gave red gums from which no satisfactory product was isolated.

4 : 4′-*Dicyanodiphenyl Ether.*—(*a*) The Sandmeyer method gave 50% of sublimed material. (*b*) In the Ullmann method, sodium 4-cyanophenoxide dried at 120° (7 g.), mixed with excess of 4-bromobenzonitrile (20 g.) and copper powder (0·1 g.), was heated to gentle ebullition (250—270°) for 3½ hours. The cooled melt was ground and washed thoroughly, first with ether and then with water. Yield 4·1 g. (37%), m. p. 178—180°. The *dinitrile* crystallised readily from alcohol (50 vols.), glacial acetic acid or pyridine (3 vols.); m. p. 180° (Found : N, 12·8. $C_{14}H_8ON_2$ requires N, 12·7%).

4 : 4′-*Dicyanodiphenyl sulphide*, similarly prepared by Sandmeyer method, formed pale yellow prisms from alcohol, m. p. 133—134° (Found : N, 12·0. $C_{14}H_8N_2S$ requires N, 11·9%).

4 : 4′-*Dicyanodiphenylsulphone.*—4 : 4′-Dicarboxydiphenylsulphone (Michael and Adair, *Ber.*, 1878, **11**, 121) was converted *via* the acid chloride into the *diamide*, m. p. >300°. Yield, 80% (Found : N, 9·4. $C_{14}H_{12}O_4N_2S$ requires N, 9·3%). The diamide was heated over a naked flame with twice its weight of phosphoric oxide until it became dark brown and sticky. The melt was extracted with 2N-sodium carbonate, and the residue crystallised from glacial acetic acid, forming faintly yellow prisms, m. p. 232—233°, identical with the product prepared from 4 : 4′-diaminodiphenylsulphone by the Sandmeyer reaction (Found : N, 10·5. $C_{14}H_8O_2N_2S$ requires N, 10·45%).

4-*Cyanodiphenyl Ether.*—4-Bromobenzonitrile (9·1 g.), boiled for 6 hours with excess of phenol (20 g.) containing potassium hydroxide (3·5 g.), gave a mixture of the required nitrile and the corresponding amide, which were separated by sublimation at 100°/0·1 mm. The nitrile, which sublimed, had m. p. 43—45° (Found : N, 7·25. $C_{13}H_9ON$ requires N, 7·2%). The residual *amide*, crystallised from 40% alcohol, had m. p. 164—165° (Found : N, 6·4. $C_{13}H_{11}O_2N$ requires N, 6·6%).

4-*Aminobenzonitrile.*—The dried ethereal extract of 4-aminobenzaldehyde obtained from 4-nitrotoluene (270 g.) (Geigy, D.R.-P. 86,874; Hodgson and Beard, J., 1927, 20) was treated with acetic anhydride (300 c.c.) and left overnight. The crude 4-acetamidobenzaldehyde (170 g., m. p. 149—150°) which separated was converted into the oxime (175 g.) (Gabriel and Herzberg, *Ber.*, 1883, **16**, 2004). The crude oxime, after drying at 100°, was boiled for 1 hour with acetic anhydride (150 c.c.). After stirring into ice-water (1 l.), the solution was neutralised; the resulting 4-acetamidobenzonitrile was collected and added to boiling 2N-hydrochloric acid (1,200 c.c.) and boiling was continued for 5 minutes after complete solution. The solution was then cooled in ice and neutralised, and the light yellow 4-aminobenzonitrile collected, washed, and dried in a vacuum. Yield 91 g., m. p. 82—84°. Acetylation of the aqueous mother-liquor with acetic anhydride gave a recovery of 4-acetamidobenzonitrile (about 16 g.). The total yield is thus 80%, calculated on 4-acetamidobenzaldehyde.

4-*Hydroxybenzonitrile.*—The Sandmeyer reaction on *p*-aminophenol is best carried out with the cuprocyanide solution at 90—95° (H. King, private communication). The most convenient method of isolation on a large scale is as follows. The acidified reaction mixture was saturated with sodium chloride, and the crude hydroxybenzonitrile collected. The wet product was extracted with ether (the solubility of the purified nitrile is approximately 40% in ether at room temperatures but only 2% in benzene), the extract washed with a little water after separation from any tarry matter, dried, and evaporated, and the residual nitrile distilled under reduced pressure. B. p. 148°/1 mm. Yield, 65—70%. The amount of nitrile remaining in the aqueous solution after salting out was approximately 5% of the total, a quantity which obviously did not merit recovery by ether extraction.

4-*Cyanophenyl* 4-*Cyanobenzyl Ether.*—To 4-hydroxybenzonitrile (24 g.), dissolved in alcohol (100 c.c.), was added a solution of sodium ethoxide (4·6 g. of sodium in 100 c.c. of alcohol), followed by 4-cyanobenzyl chloride (35 g.). The solution was refluxed for 3 hours. The mixture of salt and *dinitrile*, which separated on cooling, was washed with cold alcohol and then with water. The product at this stage was pure and needed no further crystallisation. Yield 42·2 g. (90%); m. p. 167—168° (Found : N, 12·1. $C_{15}H_{10}ON_2$ requires N, 11·95%).

3-*Cyanophenyl* 4-*cyanobenzyl ether*, obtained similarly from 3-hydroxybenzonitrile and 4-cyanobenzyl chloride, formed fine needles from alcohol, m. p. 97—98° (Found : N, 12·0. $C_{15}H_{10}ON_2$ requires N, 11·95%).

ω-*Cyano*-p-*tolyl* 4-*cyanobenzyl ether*, prepared from 4-hydroxyphenylacetonitrile and 4-cyanobenzyl chloride, and separated from a small amount of amide formed in the condensation by the sublimation process, formed short prisms from alcohol, m. p. 92° (Found : N, 11·3. $C_{16}H_{12}ON_2$ requires N, 11·3%).

4 : 4′-*Dicyano-αω-diphenoxyalkanes.*—The same general procedure was adopted throughout this series, minor variations such as volume of alcohol and time of boiling being introduced as required. For the first member of the series methylene iodide was used; in all other cases the alkylene dibromide was employed. The nitriles were well-defined crystalline solids, alcohol or acetic acid being the most convenient solvents for recrystallisation. The following details for 4 : 4′-dicyano-αγ-diphenoxypropane are typical. To a suspension of 4-hydroxybenzonitrile (48 g.) in ethyl alcohol (200 c.c.) was added a solution of sodium ethoxide (9·2 g. of sodium in 200 c.c. of alcohol), and to the resulting solution of sodium 4-cyanophenoxide was added trimethylene bromide (40 g.). The solution was refluxed for 16 hours and then cooled with stirring. The mixture of sodium

bromide and dicyano-compound was collected and washed with alcohol and then with water until free from sodium bromide. In most cases the dinitriles at this stage were sufficiently pure for conversion into the amidines. Alcoholic sodium hydroxide may be substituted for sodium ethoxide solution.

4 : 4′-*Dicyanodiphenoxymethane* (yield, 30%) formed needles from acetic acid, m. p. 148° (Found : N, 11·2. $C_{15}H_{10}O_2N_2$ requires N, 11·2%).

4 : 4′-*Dicyano-αβ-diphenoxyethane* (yield, 55%) formed prisms from acetic acid, m. p. 197° (Found : N, 10·6. $C_{16}H_{12}O_2N_2$ requires N, 10·6%).

4 : 4′-*Dicyano-αγ-diphenoxypropane* (yield 83%) crystallised from acetic acid in prisms, m. p. 188° (Found : N, 10·1. $C_{17}H_{14}O_2N_2$ requires N, 10·1%).

4 : 4′-*Dicyano-αδ-diphenoxybutane* (yield, 60%) formed prisms from acetic acid, m. p. 168—169° (Found : N, 9·75. $C_{18}H_{16}O_2N_2$ requires N, 9·6%).

4 : 4′-*Dicyano-αε-diphenoxypentane* (yield, 78%) separated from alcohol in needles, m. p. 114—114·5° (Found : N, 9·1. $C_{19}H_{18}O_2N_2$ requires N, 9·1%).

4 : 4′-*Dicyano-αζ-diphenoxyhexane* (yield, 70%) formed prisms from acetic acid, m. p. 147° (Found : N, 8·9. $C_{20}H_{20}O_2N_2$ requires N, 8·8%).

4 : 4′-*Dicyano-αη-diphenoxyheptane* (yield, 55%) formed rhombohedra from acetic acid, m. p. 107° (Found : N, 8·5. $C_{21}H_{22}O_2N_2$ requires N, 8·4%).

4 : 4′-*Dicyano-ακ-diphenoxydecane* (yield, 30%) formed needles from alcohol, m. p. 123° (Found : N, 7·4. $C_{24}H_{28}O_2N_2$ requires N, 7·4%).

1 : 4-*Di*-(4′-*cyanobenzyloxy*)*benzene* (yield, 83%) had m. p. 170—171° (Found : N, 8·0. $C_{22}H_{16}O_2N_2$ requires N, 8·2%).

ωω′-*Di*-(4′-*cyanophenoxy*)-p-*xylene* (yield, 60%) formed prisms from acetic acid, m. p. 215—216° (Found : N, 8·1. $C_{22}H_{16}O_2N_2$ requires N, 8·2%).

β-4-*Cyanophenoxyethyl Bromide*.—Ethylene dibromide (30 g.), 4-hydroxybenzonitrile (11·9 g.), sodium hydroxide (4 g.), and water (60 c.c.) were refluxed for 6 hours. After cooling, the oil was extracted with ether, filtered from a little 4 : 4′-dicyano-αβ-diphenoxyethane, washed with dilute sodium hydroxide solution, and dried. After removal of ether the residual oil was stirred with light petroleum (b. p. 60—80°). The solid obtained crystallised from alcohol in white needles, m. p. 59°. Yield, 45% (Found : N, 6·2. C_9H_8ONBr requires N, 6·2%).

4 : 4′-*Dicyano-β-phenoxyethylaniline*.—β-4-Cyanophenoxyethyl bromide (11 g.) and 4-aminobenzonitrile (11·7 g.) were heated together for 1 hour at 130—140°. After cooling, the mass was ground with water and then with alcohol. The residue crystallised from 60% acetic acid in pale yellow prisms, m. p. 163°. Yield, 35% (Found : N, 15·9. $C_{16}H_{13}ON_3$ requires N, 16·0%).

4-*Cyanobenzyl Alcohol*.—When the hydrolysis of 4-cyanobenzyl chloride by potassium carbonate solution was carried out according to Banse (*loc. cit.*), a low-melting solid, liquid in contact with water, always accompanied the product, m. p. 134°, described by Banse as the nitrile. Further examination showed that the low-melting solid was the nitrile, which on further hydrolysis gave the amide, m. p. 134—135°. If the period of hydrolysis was shortened to 2½ hours instead of the 4 hours of Banse, the yield of 4-cyanobenzyl alcohol, isolated by ether extraction and purified by vacuum distillation, was 85%. B. p. 203°/53 mm., m. p. 41—42° (Found : C, 71·9; H, 5·8; N, 10·5; *M*, ebullioscopic in benzene, 144, 147. Calc. for C_8H_7ON : C, 72·1; H, 5·3; N, 10·5%; *M*, 133). The *phenylurethane* had m. p. 112—113° (Found : N, 11·2. $C_{15}H_{12}O_2N_2$ requires N, 11·2%), and 4-*carbamidobenzyl alcohol*, m. p. 134—135° (Found : C, 63·1; H, 5·7; N, 9·4. $C_8H_9O_2N$ requires C, 63·5; H, 6·0; N, 9·3%).

4 : 4′-*Dicyanodibenzyl Ether*.—(*a*) 4-Cyanobenzyl chloride (40 g.) was boiled with potassium hydroxide solution (80 g. in 160 c.c. of water) until it had dissolved (about 3 hours). The potassium salt of 4 : 4′-dicarboxydibenzyl ether which separated on cooling was collected and dissolved in hot water, and the acid precipitated by hydrochloric acid. Yield 15 g., m. p. 272—274° (cf. Günther, *loc. cit.*). The mother-liquor from the potassium salt yielded on acidification a mixture of the above acid and 4-hydroxymethylbenzoic acid, from which 3·5 g. of the latter, m. p. 175—182°, were separated by crystallisation from hot water. The dicarboxylic acid was ground with twice its weight of phosphorus pentachloride until reaction set in and was then left for ½ hour. The mass was then ground with ice, and the crude acid chloride separated and added to 20 vols. of aqueous ammonia (*d* 0·880). After ½ hour's stirring, the *diamide* was removed. Yield, 80%. It formed plates or prisms from glacial acetic acid, m. p. 241° (Found : N, 9·8. $C_{16}H_{16}O_3N_2$ requires N, 9·85%). The crude diamide was converted into the dinitrile by boiling for ½ hour with an equal weight of phosphorus pentachloride in xylene (10 vols.). The crude product was precipitated by addition of light petroleum and was crystallised from alcohol. Yield, 37%. The product was identical with that from method (*b*).

(*b*) 4-Cyanobenzyl alcohol (2·4 g.), dissolved in absolute ethyl alcohol (5 c.c.), was treated with sodium ethoxide (0·4 g. of sodium in 8 c.c. of alcohol). The excess of alcohol was removed under reduced pressure and to the jelly of the sodium derivative was added 4-cyanobenzyl chloride (2·7 g.). The mixture was heated at 95—100° for 1 hour with stirring. The melt was ground with water and ether (10 c.c. of each), and the required *ether* collected. It formed hexagonal plates from alcohol, m. p. 97—98°. Yield, 0·95 g. (21%) (Found : N, 11·5. $C_{16}H_{12}ON_2$ requires N, 11·3%).

4-Cyanobenzaldehyde.—4-Cyanobenzyl alcohol (10 g.) in chloroform (60 c.c.) was treated at 0° with a solution of nitrogen tetroxide (10 g.) in dry chloroform (30 c.c.) and kept at room temperature in a sealed flask for 2 days. The excess of the oxides of nitrogen was removed in a vacuum, and the chloroform washed with dilute sodium carbonate solution and then with water. After drying and removal of chloroform the aldehyde (8—9 g.) was obtained in practically pure condition, m. p. 94—95°. A small amount of 4-cyanobenzoic acid was obtained by acidifying the alkaline wash liquors.

Benzoin Condensation of 4-Cyanobenzaldehyde.—A solution of 4-cyanobenzaldehyde (5 g.) in alcohol (10 c.c.) was treated with a solution of potassium cyanide (1 g.) in water (2 c.c.). Reaction was immediate and the solution darkened. After boiling under reflux for 1 hour, the crystalline *4 : 4'-dicyanodeoxybenzoin* which separated was removed and washed with alcohol. Yield, 1·8—2·0 g. (40%). It formed irregular plates from glacial acetic acid or heavy prisms from acetone, m. p. 219—220° (Found : C, 77·9; H, 4·3; N, 11·3; *M*, ebullioscopic in benzene, 264. $C_{16}H_{10}ON_2$ requires C, 78·0; H, 4·1; N, 11·4%; *M*, 246). Variation in time of boiling produced little variation in yield. Dilution of the alcoholic mother-liquors yielded a viscous gum which slowly hardened. The only product isolated from this was 4-cyanobenzoic acid (0·3 g.).

4-Cyanobenzoyl Chloride.—A mixture of 4-cyanobenzoic acid (3·3 g.) with thionyl chloride (8 c.c.) was heated for 1 hour on the steam-bath. The excess of thionyl chloride was removed in a vacuum, and the residual oil ground with ice-water. The moist solid was at once dissolved in benzene and the solution was dried, filtered, and concentrated to small bulk; addition of light petroleum gave 2 g. of crystalline *acid chloride*, m. p. 65° (Found : N, 8·95. C_8H_4ONCl requires N, 9·25%). Phosphorus pentachloride was unsatisfactory for this preparation, as it gave appreciable quantities of the acid anhydride.

4 : 4'-Dicyanobenzanilide.—Molecular proportions of 4-cyanobenzoyl chloride and 4-aminobenzonitrile in pyridine solution yielded, after the usual procedure, the required *anilide* in 85% yield. It formed colourless prisms from pyridine, m. p. 259—261° (Found : C, 73·0; H, 3·5; N, 16·9. $C_{15}H_9ON_3$ requires C, 73·0; H, 3·7; N, 17·0%).

4 : 4'-Dicyanobenzenesulphonanilide, prepared by condensing 4-cyanobenzenesulphonyl chloride and *p*-aminobenzonitrile in dry pyridine and repeatedly crystallised from 50% acetic acid, formed prisms, m. p. 201—202° (Found : N, 15·0. $C_{14}H_9O_2N_3S$ requires N, 14·8%).

β-Phenylethyl Bromide.—The following simple procedure gave excellent results. β-Phenylethyl alcohol (technical) was distilled with 2 vols. of hydrobromic acid (50% w/v) at the rate of 80—100 c.c. per hour. At first water and phenylethyl bromide collected and the upper aqueous layer was rejected. When the temperature of the vapour reached 124° the phenylethyl bromide became the upper layer and the lower layer of constant-boiling hydrobromic acid was returned to the distillation flask at convenient intervals. A continuous separator can be fitted, but it is an unnecessary elaboration unless large-scale operations are in progress. When all the bromide had distilled, it was separated, washed, dried, and redistilled, b. p. 94—95°/12—13 mm. Yield, 90%.

4-Cyanophenyl β-phenylethyl ether, obtained by condensation of β-phenylethyl bromide with sodium 4-cyanophenoxide in the usual way (yield, 20%), formed plates from alcohol, m. p. 64° (Found : N, 6·55. $C_{15}H_{13}ON$ requires N, 6·3%). Nitration in concentrated sulphuric acid at −5° gave 3-nitro-4-hydroxybenzonitrile, m. p. 143° (Found : N, 16·8. Calc. : N, 16·7%). Nitration in nitric acid (*d* 1·5) at −10° to 0° gave almost theoretical yields of *2-nitro-4-cyanophenyl 4(?)-nitro-β-phenylethyl ether*, which formed prisms from acetic acid, m. p. 185—186° (Found : N, 13·5. $C_{15}H_{11}O_5N_3$ requires N, 13·4%). Heating of this ether for ½ hour at 90° in concentrated sulphuric acid produced fission of the ether linkage and 3-nitro-4-hydroxybenzoic acid (yield, 42%) was isolated. Other attempts to achieve mononitration failed.

All attempts to condense 4-nitro-β-phenylethyl bromide with 4-hydroxybenzonitrile gave impracticably small yields of ether.

4-Amino-β-phenylethyl Bromide.—(*a*) 4-Nitro-β-phenylethyl bromide (9·6 g.) in ethyl alcohol (100 c.c.) containing 10N-hydrochloric acid (4 c.c.) and platinum oxide catalyst (Adams) (0·2 g.) was reduced with hydrogen at 50 lb. pressure at room temperature. After removal of catalyst and concentration of the solution the required *hydrochloride* was obtained by addition of ether. Yield, 9·2 g. (95%). It crystallised from absolute alcohol in prisms, m. p. 212—213° (Found : N, 5·9. $C_8H_{10}NBr,HCl$ requires N, 5·8%). The sulphate was much less soluble in water, and formed plates from dilute sulphuric acid.

(*b*) 4-Nitro-β-phenylethyl bromide (4·6 g.) was added to a solution of stannous chloride (14 g.) in hydrochloric acid (20 c.c., *d* 1·16) and warmed for a short time at 80—90° until all the oil had disappeared. The solution was cooled and filtered from a trace of unchanged material which separated, and the stannichloride was then crystallised by the addition of 3—4 vols. of 10N-hydrochloric acid. The product was removed, dissolved in water, made alkaline with excess of sodium hydroxide at 0—5° and rapidly extracted with ether. The extract was washed, dried, and treated with alcoholic hydrogen chloride. The hydrochloride so obtained was identical with that from (*a*). Yield, 55%.

4-Cyano-β-phenylethyl Bromide.—The Sandmeyer reaction on the above amine was carried out at 20—30° in presence of benzene. The benzene layer and extracts were washed, dried, and distilled. The fraction, b. p. 135—140°/2 mm., was collected. Yield, 40%. The *nitrile* crystallised from 30 vols. of light petroleum (b. p. 40—60°) in long slender prisms, m. p. 53° (Found : N, 6·5; Br, 37·5. C_9H_8NBr requires N, 6·7; Br, 38·0%). This product and the amine have an irritant action on the skin.

4-Cyanophenyl 4-cyano-β-phenylethyl ether, obtained in 10—12% yield by condensation of the preceding nitrile with 4-hydroxybenzonitrile, formed colourless prisms from alcohol, m. p. 129—130° (Found: N, 11·1. $C_{16}H_{12}ON_2$ requires N, 11·3%).

N-4-*Cyanophenylbenziminochloride*.—*N*-Benzoyl-4-cyanoaniline (32 g.) was ground with phosphorus pentachloride (33 g.) and heated for 1 hour at 120°. The phosphorus oxychloride was removed by distillation at 25 mm. pressure, the residual syrup dissolved in cold benzene (40 c.c.) and the solution filtered from a little impurity and distilled. Benzene and a little phosphorus pentachloride were removed and the *product* was collected at 194—198°/3 mm. Yield, 27 g. (76%). It crystallised from light petroleum (b. p. 60—80°) in fine prisms, m. p. 88—89° (Found: N, 11·8. $C_{14}H_9N_2Cl$ requires N, 11·65%).

N-4-*Cyanophenylbenzimino-4'-cyanophenyl Ether*.—The iminochloride (27 g.) was dissolved in dry ether (200 c.c.), added to a cold solution of sodium 4-cyanophenoxide (sodium, 2·7 g.), and kept overnight. The mixture of sodium chloride and the *ether* was collected and washed with alcohol and then with water. Yield, 32 g. (82%). The product was pure, m. p. 155° (Found: N, 13·1. $C_{21}H_{13}ON_3$ requires N, 13·0%). Rearrangement to N-*benzoyl*-4 : 4'-*dicyanodiphenylamine* took place smoothly when the iminoether was heated for 1½ hours at 280—300°. The product formed heavy rhombic crystals, m. p. 219°, from 15 vols. of acetic acid (Found: N, 13·0. $C_{21}H_{13}ON_3$ requires N, 13·0%).

4 : 4'-*Diamidinodiphenylamine dihydrochloride* was obtained from the corresponding dinitrile. This was pale yellow, neutral, and readily soluble in water (Found: N, 20·2, 20·4. $C_{14}H_{15}N_5,2HCl,H_2O$ requires N, 20·3%). Its solution with excess of 2N-sulphuric acid gave heavy, deep orange rhombs of the sparingly soluble *acid sulphate* (Found: N, 17·7. $C_{14}H_{15}N_5,1\frac{1}{2}H_2SO_4$ requires N, 17·5%).

4 : 4'-*Diamidino*-N-*benzoyldiphenylamine*.—The aqueous solution of crude amidine hydrochloride obtained in the usual preparation from the corresponding dinitrile was treated with an excess of 2N-sulphuric acid to remove any dibenzoylated amidine as the sparingly soluble sulphate (see above). The acid mother-liquor yielded the *N*-benzoylated *base* on precipitation with alkali, a small intermediate fraction of less basic matter being removed first. This formed colourless flat prisms which retained water of crystallisation after drying in a vacuum; m. p. 194° (decomp.) (Found: N, 17·0; loss at 100—110°/1—2 mm., 10·4. $C_{21}H_{19}ON_5,2\frac{1}{2}H_2O$ requires N, 17·4; H_2O, 11·2%). When the anhydrous amidine (107 mg.) was heated at 180—200°, and the product sublimed, benzamide (30 mg., 82%), m. p. 127—128°, was collected first and then 4 : 4'-dicyanodiphenylamine (50 mg., 76%), m. p. 240—246°.

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21. *Rubber, Polyisoprenes, and Allied Compounds. Part I. The Synthesis of Low-molecular Polyisoprenes of the Rubber and the Squalene Type.*

By ERNEST HAROLD FARMER and DONALD A. SUTTON.

A synthesis for dihydrofarnesene, $H\cdot[CH_2\cdot CMe{:}CH\cdot CH_2]_3\cdot H$, has been devised which appears to be capable of utilisation in the formation of other low-molecular dihydropolyisoprenes,

$$H\cdot[CH_2\cdot CMe{:}CH\cdot CH_2]_n\cdot H,$$

in which the individual isoprene units are uniformly arranged in head-to-tail fashion. This synthesis, starting from geraniol, gives a triene hydrocarbon which differs in one of its additive properties from a product described as dihydrofarnesene in the literature. The reason for the difference has been investigated.

A new synthesis for squalene has been devised which appears to be capable of utilisation in the formation of other symmetrical dihydropolyisoprenes, $H\cdot[CH_2\cdot CMe{:}CH\cdot CH_2]_n\cdot[CH_2\cdot CH{:}CMe\cdot CH_2]_n\cdot H$, of the squalene type. This starts from geranylacetone and the Grignard derivative from 1 : 4-dibromobutane.

FOR various purposes in connexion with the investigation of rubber it has been desired to obtain low-molecular, open-chain polyisoprenes in which a uniform head-to-tail arrangement of the isoprene units is strictly maintained. A dimeric rubber in the form of dihydromyrcene,

$$H\cdot(CH_2\cdot CMe{:}CH\cdot CH_2\cdot CH_2\cdot CMe{:}CH\cdot CH_2)\cdot H,$$

is obtainable by reduction of the myrcene hydrocarbon present in Bay oil (*Pimenta acris*), and a hexameric

polyisoprene is available in the form of squalene, a well-known component of certain fish-liver oils; but in the latter case the hydrocarbon is not of the rubber type, since the head-to-tail arrangement of C_5-units extends only from each end of the molecule to the middle. No other low-molecular, open-chain polyisoprenes, save one which is discussed below, are known, and there is no general method of passing with structural certainty up the polyisoprene series.

The possibility of obtaining a useful selection of relatively low-molecular, straight-chain polyisoprenes from isoprene itself by direct polymerisation has been examined concurrently with this work, but the triple requirement of rigid maintenance of the head-to-tail arrangement of units, the exclusion of all chain-branching arising from the 1 : 2-additive tendency of the diene molecules, and the fairly precise regulation of the chain-length, is a severe handicap to success. The obvious synthetic alternative to the polymeric method, amounting to the building-up of the chain unit by unit by formal organic methods, could not be other than laborious and expensive, and hence it seemed useful before embarking on it to explore the possibility of applying a third procedure, based on the Wurtz and the Grignard reaction.

Bifunctional Grignard reactions have been known in the saturated series for many years. Von Braun and Sobecki (*Ber.*, 1911, **44**, 1921) described C_8- and C_{12}-hydrocarbons obtained by such means from 1 : 4-dibromobutane, and Carothers and his co-workers have since described numerous such reactions and have closely studied the conditions necessary for promoting the polymolecular type of reaction (*J. Amer. Chem. Soc.*, 1929, **51**, 2548; 1930, **52**, 5279; *Chem. Rev.*, 1931, **8**, 353). Attempts, however, to employ an unsaturated dihalide have led so invariably and so completely to the monomeric butadiene by all feasible methods of carrying out the Wurtz and the Grignard reaction that further attempts in this direction have been abandoned.

Rubber Type of Hydrocarbon.—The most promising approach to unit-by-unit synthesis of straight-chain polyisoprenes of the rubber type seemed to be that afforded by Ruzicka's elegant procedure for building up polyterpene alcohols. From geraniol, he passed by the successive action of phosphorus trichloride, acetoacetic ester, acetylene, and nascent hydrogen to a tertiary tri-isoprene alcohol, nerolidol, and thence with phosphorus tribromide to the bromide of its anionotropic (primary alcoholic) counterpart, farnesyl bromide :

$$\underset{\text{Geraniol}}{\text{Ger.}\cdot OH} \longrightarrow \text{Ger.}\cdot Cl \longrightarrow \underset{\text{Geranylacetone}}{\text{Ger.}\cdot CH_2\cdot CO\cdot CH_3} \longrightarrow \underset{\text{Dehydronerolidol}}{\text{Ger.}\cdot CH_2\cdot CMe(OH)\cdot C{:}CH} \longrightarrow$$

$$\underset{\text{Nerolidol}}{\text{Ger.}\cdot CH_2\cdot CMe(OH)\cdot CH{:}CH_2} \longrightarrow \underset{\text{Farnesyl bromide}}{\text{Ger.}\cdot CH_2\cdot CMe{:}CH\cdot CH_2Br}$$

$$[\text{Ger.} = CH_3\cdot CMe{:}CH\cdot CH_2\cdot CH_2\cdot CMe{:}CH\cdot CH_2\cdot.]$$

Further, while the present work was in progress he has, by the same method, synthesised the tetra-isoprene alcohol, geranylgeraniol, $C_{20}H_{33}\cdot OH$, from its naturally occurring tri-isoprene analogue, farnesol. Thus it has been demonstrated that it is possible to pass from the C_{10}- to the C_{15}- and thence to the C_{20}-polyisoprene skeleton in the case of alcohols; and further application of the method appears to be limited only by the necessity for using increasingly large quantities of starting material as the series is ascended.

If a ketone of Ruzicka's series, *e.g.*, geranylacetone or farnesylacetone, were to be submitted to the action of a Grignard reagent, a tertiary alcohol might be expected to result, which by dehydration ought to lead to one or more of three hydrocarbons. One of these hydrocarbons should have the correct structure for a member of the straight-chain hydrogen-stabilised (*i.e.*, dihydro) polyisoprene series. We have found that geranylacetone yields smoothly with ethylmagnesium bromide a tertiary alcohol,

$$\text{Ger.}\cdot CH_2\cdot CO\cdot CH_3 \longrightarrow \text{Ger.}\cdot CH_2\cdot CMe(OH)\cdot CH_2\cdot CH_3 \xrightarrow{-H_2O}$$

$$\text{Ger.}\cdot CH_2\cdot CMe{:}CH\cdot CH_3 \text{ or } \text{Ger.}\cdot CH{:}CMe\cdot CH_2\cdot CH_3 \text{ or } \text{Ger.}\cdot CH_2\cdot CEt{:}CH_2$$

dihydronerolidol, which by dehydration with potassium bisulphate yields a triolefinic hydrocarbon, $C_{15}H_{26}$. This hydrocarbon gives on ozonolysis acetaldehyde and acetic acid in fairly good yield, but no detectable trace of formaldehyde, formic acid, or methyl ethyl ketone. Furthermore, it gives with dry hydrogen chloride a 93% yield of a homogeneous trihydrochloride. Now, although all the three isomeric hydrocarbons would be likely to yield in large measure, and probably completely, the same form of the trihydrochloride, yet the ozonolysis result points plainly to the fact that the dehydration product of dihydronerolidol is a pure, or at any rate a substantially homogeneous, *dihydrofarnesene*,

$$H\cdot[CH_2\cdot CMe{:}CH\cdot CH_2]_3\cdot H,$$

which represents the (hydrogen-stabilised) tri-isoprene member of the rubber series; also there seems little doubt that application of the same procedure to geranylgeraniol will yield the corresponding tetra-isoprene, $H\cdot[CH_2\cdot CMe{:}CH\cdot CH_2]_4\cdot H$—a result which it is hoped to be able to report later.

Soon after the above experiments had been completed, however, it was found that Jones and Haenke (*Proc. Roy. Soc. Queensland*, 1936, **48**, 20, 41) in examining essential oils derived from Queensland flora had isolated a nerolidol fraction, from which in the course of purification by conversion into the sodium salt they had obtained as by-product a hydrocarbon, $C_{15}H_{26}$, having $d^{15\cdot5^\circ}$ 0·8335, $n_D^{20^\circ}$ 1·4700. This hydrocarbon they concluded to be dihydrofarnesene, since linalool under similar treatment gave dihydromyrcene, and they characterised it by forming a solid hexabromide, m. p. 131°. To confirm the constitution assigned they prepared for comparison a reputed dihydrofarnesene by the reduction with sodium and alcohol of farnesene derived by dehydration of nerolidol. This hydrocarbon also gave the hexabromide, m. p. 131°.

This property of giving amongst the various stereoisomeric forms likely to arise from an unconjugated tri-isoprene a *solid* hexabromide, and also the values assigned to the density and refractive index, distinguish the hydrocarbon from that described above, which had $d_{4^\circ}^{20^\circ}$ 0·8202, $n_D^{20^\circ}$ 1·4712, and did not give a solid hexabromide.

We had realised at the outset that farnesene derived by dehydration of farnesol was unlikely ever to be entirely free from its cyclic triene isomeride, bisabolene, since it cyclises so easily with acid reagents, among which must be included the potassium bisulphate probably employed by Jones and Haenke. Kerschbaum (*Ber.*, 1913, **46**, 1732) had dehydrated farnesol by heating it with potassium bisulphate and obtained a hydrocarbon which Ruzicka (*Helv. Chim. Acta*, 1923, **6**, 498) subsequently demonstrated to be not farnesene but bisabolene. Ruzicka, however, obtained a product with better physical constants ($d_{4^\circ}^{18^\circ}$ 0·8385; $n_D^{18^\circ}$ 1·4965), which he concluded to be farnesene, by distilling off the hydrocarbon from the bisulphate as it was formed; he suggested that farnesene must be $C_{10}H_{17}\cdot CH{:}CMe\cdot CH{:}CH_2$, or

$$C_{10}H_{17}\cdot CH_2\cdot C(:CH_2)\cdot CH{:}CH_2,$$

or a mixture of both. Later, he synthesised bisabolol (*ibid.*, 1932, **15**, 3). Farnesene having either of the (conjugated) structures suggested by Ruzicka should, of course, give the desired dihydrofarnesene on reduction.

Whether farnesene can be obtained entirely free from bisabolene when potassium bisulphate is used as dehydrating agent does not appear from Ruzicka's observations. We have dehydrated farnesol with this reagent, distilling off the hydrocarbon as it was formed, and so obtained a product having rather a higher density ($d_{4^\circ}^{19\cdot5^\circ}$ 0·8469; $n_D^{19^\circ}$ 1·4945) and probably therefore a rather greater bisabolene content than Ruzicka's. Determination of the unsaturation of this hydrocarbon by hydrogenation gave a value, probably somewhat low through incompleteness of reaction, of $|\overline{=}_{3\cdot5}$ per $C_{15}H_{24}$, indicating the presence therein of at least 50% of farnesene; heating with formic acid (Ruzicka's method) caused complete conversion into bisabolene, as shown by the purity of the derived bisabolene trihydrochloride. Reduction of the hydrocarbon with sodium and alcohol gave a " dihydrofarnesene " having three double bonds (Found, by hydrogenation : $|\overline{=}_{2\cdot85}$) and physical constants somewhat higher than those of our hydrocarbon from dihydronerolidol, doubtless due to the substantial amount of bisabolene present; but the physical constants of this reduction product agreed closely with those of Jones and Haenke's material. Conversion of this " dihydrofarnesene " into the hydrochloride gave a solid product which was easily separated into two trihydrochlorides, one of bisabolene and one identical with the *trihydrochloride* of our dihydrofarnesene from dihydronerolidol. Nevertheless, we have not yet isolated from the bromide of this " dihydrofarnesene " any crystalline hexabromide. We see no reason, therefore, to doubt the substantial purity of our dihydrofarnesene described above, or the correctness of the constitution assigned to it.

Squalene Type of Hydrocarbon.—With farnesyl bromide as starting point, it is only necessary, as Karrer has shown (*Helv. Chim. Acta*, 1931, **14**, 78) to couple the hydrocarbon radicals of two molecules of halide by a metal such as magnesium to produce a hydrocarbon identical with natural squalene. Starting, however, from the more readily available geraniol, it is necessary to intercalate a centrosymmetrical di-isoprene system between two geranyl radicals. This might be expected to be capable of accomplishment, so far as the carbon framework is concerned, by combining two molecules of geranylacetone with the Grignard reagent derived from 1 : 4-dibromobutane :

$$2\text{Ger.}\cdot CH_2\cdot COMe + MgBr\cdot[CH_2]_4\cdot MgBr \longrightarrow \text{Ger.}\cdot CH_2\cdot CMe(OH)\cdot[CH_2]_4\cdot CMe(OH)\cdot CH_2\cdot\text{Ger.}$$

(Ger. = $C_{10}H_{17}$)

As regards the Grignard reagent required, von Braun and Sobecki's experiments (*loc. cit.*) indicated that the metallo-organic derivatives $MgBr\cdot[CH_2]_4\cdot MgBr$, $MgBr\cdot[CH_2]_8\cdot MgBr$, and $MgBr\cdot[CH_2]_{12}\cdot MgBr$ are all formed side by side when magnesium acts on 1 : 4-dibromobutane; also Young, Prater, and Winstein (*J. Amer. Chem. Soc.*, 1933, **55**, 4908) have described optimum conditions for the preparation of the normal Grignard compound from the difficultly reactive crotyl bromide. Since the Grignard

product from dibromobutane cannot easily be fractionated before use, we tried to suppress as far as possible the formation of polymeric forms of the metallo-organic compound from 1 : 4-dibromobutane by using the conditions described by Young and his co-workers. This procedure, probably aided by the preferential tendency for the monomeric rather than the polymeric forms of the dimagnesium halide to react with the geranylacetone, has been successful in yielding principally *one* compound—a *glycol* of the expected empirical formula, $C_{30}H_{52}(OH)_2$; there was, however, a residue which probably consisted of the analogous C_{34}-glycol derived from $MgBr{\cdot}[CH_2]_8{\cdot}MgBr$.

The C_{30}-glycol showed a molecular refraction 1·5 units higher than the calculated figure, which recalls the exactly similar experience of Heilbron with non-conjugated natural squalene (J., 1936, 1630; see also Farmer and Sutton, this vol., p. 139) and of Farmer and Van den Heuvel (*J. Soc. Chem. Ind.*, 1938, **57**, 24) with highly unsaturated fish-oil acids. This phenomenon, which is apparently due either to the inaccuracy of the atomic refractivity values (Eisenlohr's) employed in calculating $[R_L]_D$, or to the appearance of conjugation during heating, is being investigated.

By the action of dry hydrogen chloride on the C_{30}-glycol there was obtained a mixture of three isomeric hexahydrochlorides which proved to be identical with the three isomerides first obtained by Heilbron from squalene (*loc. cit.*); and since squalene can easily be regenerated from these hydrochlorides by the action of mildly alkaline reagents, this work constitutes a new synthesis of squalene and also suggests a general method for the synthesis of hydrocarbons of the squalene type. Thus, from farnesylacetone a

$$2Far.{\cdot}CH_2{\cdot}COMe + MgBr{\cdot}[CH_2]_4{\cdot}MgBr \longrightarrow Far.{\cdot}CH_2{\cdot}CMe(OH){\cdot}[CH_2]_4{\cdot}CMe(OH){\cdot}CH_2{\cdot}Far.$$

[Far. = $C_{15}H_{25}$.]

C_{40}-glycol would be expected to result, from which by direct dehydration, or *via* the derived octahydrochlorides, a C_{40}-polyisoprene hydrocarbon of squalene type might be expected to be formed.

It is on record (Simonsen, " The Terpenes," Vol. 2, 562) that farnesol gives with dry hydrogen chloride the same product as does its dehydration product farnesene :

$$\underset{\text{Farnesol}}{H{\cdot}[CH_2{\cdot}CMe{:}CH{\cdot}CH_2]_3{\cdot}OH} \xrightarrow{HCl} \text{Tetrahydrochloride} \xleftarrow{HCl} \underset{\text{Farnesene}}{H{\cdot}[CH_2{\cdot}CMe{:}CH{\cdot}CH_2]_2{\cdot}CH{:}CMe{\cdot}CH{:}CH_2}$$

The new C_{30}-glycol, as noted above, gives the same mixture of three isomeric hexahydrochlorides as does natural squalene. To this we now add that the dihydronerolidol whose synthesis is described above gives the same trihydrochloride as does its dehydration product dihydrofarnesene. The yield of hydrochloride from the alcohol was quantitative, whereas that from the hydrocarbon at the first attempt was 93%; and it is of considerable interest that the yields of hydrochlorides of polyisoprenes (including rubber with a molecular weight of about 300,000) seem generally to be quantitative, or very nearly so, under suitable conditions of reaction.

Experimental.

Geranylacetone.—Commercial geraniol of good quality was purified by conversion into its calcium chloride compound, essentially the procedure of Bertram and Gildemeister (*J. pr. Chem.*, 1897, **56**, 506) being used. The regenerated geraniol, b. p. 117°/13 mm. (yield 55—60%), was converted into its chloride (yield 60%) and thence into geranylacetone by the method of Ruzicka (*Helv. Chim. Acta*, 1923, **6**, 492). The rectified ketone boiled at 126—128°/10 mm.; yield 70%.

Dihydronerolidol.—To an ethereal solution of ethylmagnesium bromide (6·07 g. of magnesium, 27·2 g. of ethyl bromide, 100 c.c. of ether) contained in a 1-l. flask fitted with condenser, dropping funnel, and a mercury-sealed stirrer, a solution of 48·5 g. of geranylacetone in 50 c.c. of ether was added gradually with good stirring. The reaction product was boiled for 30 mins. and then decomposed by gradual addition of excess of water under good stirring. The stirring was continued whilst sufficient 2N-hydrochloric acid was added to dissolve the magnesium hydroxide, after which the crude dihydronerolidol was extracted with ether, the extract washed in turn with sodium bicarbonate solution and water, and then dried over potassium carbonate. Removal of the solvent gave a product which after suitable fractionation boiled at 137—140°/8 mm.; yield 77%. The *dihydronerolidol* was a colourless, odourless, not very mobile liquid; $d_4^{20°}$ 0·8693; $n_D^{20°}$ 1·4690; $[R_L]_D$ 71·73 (Calc. for $|_2^=$, 72·06) (Found : C, 80·5; H, 12·7; active H, 0·49. $C_{15}H_{28}O$ requires C, 80·35; H, 12·5; active H, 0·45%).

Dihydrofarnesene.—Dihydronerolidol (20 g.) was refluxed over finely powdered potassium bisulphate for 45 mins. at 18 mm. pressure in a 100 c.c. flask fitted with capillary bubbler (bath temp. 160°). The condenser was replaced by a still-head and the liquid product distilled off. The distillate (b. p. 130—140°/15 mm.) was again refluxed at reduced pressure (for 25 mins.) with 5 g. of fresh potassium bisulphate, and the product distilled off. The distillate was carefully fractionated over sodium in an apparatus based on that described by Schrader and Ritzer (*Ind. Eng. Chem. Anal.*, 1939, **11**, 54), but modified to avoid the strong tendency to

evaporative distillation experienced with the apparatus when good oil-pump vacua are employed, and provided with alternative sets of collecting cups. The bulk of the product boiled at 129—131°/11 mm. (yield 65%), leaving a liquid residue of higher b. p. The former was a triolefinic hydrocarbon, *dihydrofarnesene* (Found: C, 86·8; H, 12·7. $C_{15}H_{26}$ requires C, 87·3; H, 12·7%); $d_4^{20°}$ 0·8202, $n_D^{20°}$ 1·4712, unsaturation (iodine value) $\overline{|}_{2·99}$, $\overline{|}_{2·97}$, $[R_L]_D$ 70·29 (Calc. for $\overline{|}_3$, 70·07).

Dihydrofarnesene Trihydrochloride.—(i) *From dihydrofarnesene.* The hydrocarbon (3·25 g.), dissolved in dry ether (25 c.c.) and protected against atmospheric moisture, was saturated at 0° during 1 hour with dry hydrogen chloride. The ether and excess hydrogen chloride were evaporated, leaving a thick, oily residue which soon solidified in a vacuum desiccator. The crystals of crude *trihydrochloride* (93% yield) melted at 44—47°, but reached a constant m. p. of 52° after one recrystallisation from methyl alcohol (Found: Cl, 33·75. $C_{15}H_{29}Cl_3$ requires Cl, 33·70%).

(ii) *From dihydronerolidol.* Dihydronerolidol (3 g.), dissolved in dry ether (100 c.c.), when saturated with dry hydrogen chloride as above, gave a white solid (4·2 g.; 100%) of m. p. 44—47°, which after one crystallisation from methyl alcohol melted constantly at 52°. Mixed m. p. with foregoing trihydrochloride, 52°.

Ozonolysis of Dihydrofarnesene.—The hydrocarbon (2·9 g.), dissolved in ethyl acetate (20 c.c.) and cooled in an ice–salt bath, was ozonised (1·44 g. ozone per hour) for 90 mins., after which the solvent was removed under reduced pressure with gentle warming, and the residue decomposed by warming and finally boiling with water. The issuing gases were passed through a liquid-air trap, and the steam distillate fractionated under a short column. The products were: (1) acetone, 0·33 g. (estimated by Messenger's method), identified by 2 : 4-dinitrophenylhydrazone, m. p. 125°; (2) acetone peroxide, m. p. 130°, 50 mg. (total yield of acetone, 47%); (3) acetaldehyde, converted with considerable loss into its dimedon derivative, m. p. 139° (yield 10%); and (4) an aqueous residue containing acetic acid. Half the aqueous residue was neutralised with standard sodium ethoxide solution (3 g./l.), and the neutral solution heated with *p*-bromophenacyl bromide. The titre and the yield of *p*-bromophenacyl acetate (m. p. 83°, mixed m. p. 84—85°) both corresponded to 0·2 g. of acetic acid. The remainder of the aqueous residue gave by extraction with ether a rather viscous liquid which, by reason of its strong iodoform reaction and the formation of a semicarbazone (m. p. 183°, decomp.), was doubtless impure lævulic acid (semicarbazone, m. p. 187°). No formaldehyde could be isolated from, or detected by colour tests in, the condensate in the liquid-air trap or the volatile distillate; and likewise no methyl ethyl ketone could be isolated or detected.

Dehydration of Farnesol.—The farnesol, supplied by C. Naef and Co. of Geneva, was purified by conversion into its hydrogen phthalate and subsequently distilled. The pure alcohol (yield 40%) boiled at 118—120°/1 mm., and was characterised by converting it into farnesal (semicarbazone, m. p. 125°) as recommended by Ruzicka.

Farnesol (10 g.) was heated with finely powdered potassium bisulphate under 12 mm. pressure in a flask placed in a bath maintained at 160—170°, the hydrocarbon being allowed to distil as it was formed. The product was a yellow oil, which on redistillation over sodium boiled at 127—130°/12 mm. and had $d_4^{19·5°}$ 0·8469, $n_D^{19°}$ 1·4945; yield 4·7 g.

A portion of this dehydration product (1 c.c.) was converted into bisabolene by heating it with 90% formic acid (2 c.c.) at 120—130° for 15 mins. The product, when isolated, was an oil, b. p. 130°/15 mm., which when treated with dry hydrogen chloride in ethereal solution gave the hydrochloride. This when once recrystallised from methyl alcohol gave the correct m. p. (79°) for bisabolene trihydrochloride. Another portion (0·1004 g.) was hydrogenated in acetic acid (Adams's catalyst) and took up an amount of hydrogen (37·8 c.c. at N.T.P.) corresponding to $\overline{|}_{3·5}^{=}$ per $C_{15}H_{24}$.

Reduction, Hydrogenation, and Hydrochlorination of Dehydration Product.—A portion of the dehydration product (3·4 g.) was dissolved in absolute alcohol (30 c.c.) and reduced vigorously with lump sodium (9 g.). When ebullition slackened, the reaction vessel was heated on a water-bath and more alcohol (50 c.c.) was added. The product, isolated in the usual way and distilled over sodium, was an oil; b. p. 120—130°/12 mm., $d_4^{20°}$ 0·8348, $n_D^{22°}$ 1·4786. Another portion (0·1854 g.) when hydrogenated as above absorbed hydrogen (58 c.c. at N.T.P.) corresponding to $\overline{|}_{2·85}^{=}$.

A third portion (1 c.c.) was dissolved in dry ether and saturated with dry hydrogen chloride at 0°. The crude hydrochloride (m. p. 50—56°) was fractionally crystallised from methyl alcohol, and so gave a less soluble hydrochloride, m. p. 77°, and a more soluble one, m. p. 49—41°. The former when mixed with authentic bisabolene trihydrochloride (m. p. 79°) gave m. p. 77°, and the latter when mixed with the trihydrochloride of the hydrocarbon derived by dehydration of dihydronerolidol (see above) gave m. p. 50—51°.

Bromide of Dihydrofarnesene.—Samples of dihydrofarnesene, derived (a) by dehydration of dihydronerolidol and (b) by reduction of the farnesene–bisabolene mixture from farnesol, were dissolved in chloroform and treated with slight excess of bromine in chloroform at 0° and subsequently at room temperature. The bromides were unsolidifiable thick oils.

Synthesis of Squalene Hexahydrochlorides.

Grignard Derivative from 1 : 4-*Dibromobutane.*—1 : 4-Butylene glycol, derived from ethyl succinate (Muller, *Monatsh.*, 1927, **48**, 523, 735; 1928, **49**, 27), was converted by hydrogen bromide into 1 : 4-dibromobutane (Muller, *loc. cit.*) and thence into the corresponding dimagnesium halide under Braun and Sobecki's conditions

(*loc. cit.*) as modified by Young (*loc. cit.*) in order to avoid the formation of considerable yields of dimeric and trimeric products.

To magnesium (8·64 g.), covered with dry ether, 1 : 4-dibromobutane (38·4 g.), dissolved in ether (80 c.c.), was very slowly added with rapid stirring. Refluxing occurred, and when it subsided, more ether (150 c.c.) was added, and the whole heated on a water-bath to refluxing for ½ hour. Little of the magnesium remained, and the Grignard complex separated out as a heavy oil.

Dihydroxydihydrosqualene.—Geranylacetone (46 g.; ⅔ of theory), dissolved in ether (50 c.c.), was added gradually with good stirring to the foregoing Grignard derivative. Refluxing set in, and the reaction was completed by maintaining gentle ebullition on a water-bath for ¾ hour. The greenish product was decomposed by cautious addition of water, and the crude glycol so formed extracted from the aqueous liquor (without acidification) with ether. The ethereal extract, dried over potassium carbonate, yielded a light yellow oil (40 g.), which gave by distillation under 1 mm. pressure the fractions: (i) b. p. 80—175°, 13·4 g.; (ii) b. p. 220—250°, 24·1 g.; and (iii) brown, semi-solid residue, 2 g. The fraction (ii) was a nearly colourless, somewhat viscous oil, which on redistillation at 1 mm. pressure gave a colourless oil, b. p. 220—235° (18 g.), and a more viscous liquid, b. p. 240—250°, which was rejected. The former, *dihydroxydihydrosqualene* (Found: C, 80·35; H, 12·3. $C_{30}H_{54}O_2$ requires C, 80·7; H, 12·2%), had $d_4^{20°}$ 0·9079, $n_D^{20°}$ 1·4944, $[R_L]_D$ 143·2 (Calc.: 141·7); active H, 0·42 (Calc.: 0·45%); the latter appeared to be a mixture containing a little dihydroxydihydrosqualene and a similar material probably derived from the C_8-Grignard derivative.

Squalene Hexahydrochlorides.—Through dihydroxydihydrosqualene (5 g.), dissolved in dry ether, cooled in ice-salt and protected from moisture, a slow stream of dry hydrogen chloride was passed until the gas began to escape freely, and then for a further 15 mins. The solvent and excess of hydrogen chloride were removed at reduced pressure, whereupon the residue soon crystallised. The white crystalline mass (m. p. 100—120°), after being washed with ether, had chlorine content 33·8% (Calc. for $C_{30}H_{56}Cl_6$: 33·7%). This was separated into three isomeric hexahydrochlorides, m. p.'s 107°, 112—115°, 144°, by the procedure of Heilbron *et al* (*loc. cit.*): the isomerides (respectively) showed no depression of m. p. when mixed with the corresponding derivatives of similar m. p. obtained for comparison by treatment of genuine squalene from shark oil (*Symnorhinus lichia*) with hydrogen chloride.

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22. *The Course of Autoxidation Reactions in Polyisoprenes and Allied Compounds. Part I. The Structure and Reactive Tendencies of the Peroxides of Simple Olefins.*

By Ernest Harold Farmer and Alvappillai Sundralingam.

Criegee's conclusion that the peroxide formed by the interaction of molecular oxygen with *cyclo*hexene is a hydroperoxide in which the olefinic unsaturation survives is confirmed. The peroxides formed similarly from 1-methyl- and 1 : 2-dimethyl-*cyclo*hexene are also olefin hydroperoxides. The formation of hydroperoxides from olefins and unconjugated polyolefins in general is one of a group of important olefinic reactivities due to the lability of the hydrogen atoms of methylene groups in the α-position to the double bonds.

The hydroperoxide groups decompose spontaneously, and also by the action of heat, giving (*a*) cyclic epoxides and alcohols, (*b*) oxidation products, and (*c*) oxygenated polymeric products. In this decomposition the hydroperoxide groups act as active oxidising agents, attacking the carbon chain at the double bond, themselves reverting to hydroxyl groups. Ketones are not formed in recognisable amounts by the spontaneous decomposition of the cyclic hydroperoxides, although they have long been known to appear among the autoxidation products of mono-olefinic terpenes; they are formed, however, to a considerable extent by the violent decomposition promoted by an organic ferrous salt.

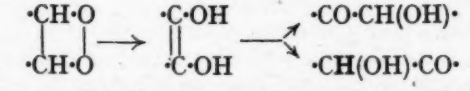
The decomposition of the olefin hydroperoxides by sulphuric acid, by superheated water, and by alkali has been examined in some detail, the first two reagents causing extensive oxidation of the carbon chain, and the last extensive hydrolysis of the hydroperoxide together with some oxidation. The nature of the products obtained in the sulphuric acid decomposition suggests a reason for the strong promoting influence of organic acids when present during olefin autoxidations.

The mechanisms of the hydroperoxide decompositions and of the complementary oxidation reactions are considered; also the manner of formation of the polymeric products, which doubtless involves the same fundamental reactivities as are involved in the drying of unsaturated oils.

THE structural changes which occur in olefinic substances when they undergo oxidation by molecular oxygen have never been elucidated, although many of these changes, such as the autoxidation of drying oils and of rubber, are of enormous practical importance. It has commonly been supposed that absorption of molecular oxygen occurs at some or all of the ethylenic centres to give peroxidic groupings, which, for want of a better representation and following Engler's suggestion (*Ber.*, 1897, **30**, 1669; 1898, **31**, 3046; 1900, **33**, 1090), have been formulated as cyclic structures $\begin{matrix}C-C\\ | \quad |\\ O-O\end{matrix}$. There is, however, little direct evidence supporting such a formulation beyond (1) that the unsaturation of the autoxidised substance usually decreases progressively (although not in quantitative correspondence) as oxygen-intake increases, and (2) that frequently the reaction ends in hydroxylation of the double bond to yield a 1 : 2-glycol, or in complete scission of the carbon chain at the double bond. The peroxidic groupings, as is well attested, show a tendency to decay, with formation from the peroxidised olefin of one or more of a wide variety of oxygenated materials, including olefin oxides, ketones, glycols, ketols, miscellaneous oxygenated materials of unknown structure (but important in the drying oils, since they seem to be largely responsible for the formation of films and skins), and, as the result of chain-scission, aldehydes, ketones, carboxylic acids, and hydroxy-carboxylic acids. If it be assumed that all these types of product, as well as certain simple degradation products such as water, carbon dioxide, and the lower fatty acids, arise from simple peroxides of the original olefins, it becomes difficult on the basis of present information to fit them into a coherent scheme and to reconcile many apparently discordant observations.

In attempting to devise such a scheme, consideration must necessarily be given to the effect on the course of reaction of the somewhat varied ways in which the autoxidations can be promoted and the conditions under which they are conducted. The most important influences seem to be catalytic agents or agencies and the temperature conditions. Many different organic, inorganic, and metallic catalysts, as well as light of different wave-lengths, have been used to initiate and facilitate autoxidation, and it is to be noted that the manner of their application may have important effects on the final products; also, raising the temperature above room-temperature is recognised generally to accelerate reaction. Whether either catalytic influences or the conditions of reaction can ever influence the character of the primary oxidation reactions (as distinct from controlling the purely secondary autoxidative changes), however, is not known with certainty. In most autoxidation reactions it is fairly clear that reaction begins with the absorption of oxygen and the immediate production of peroxide groups; in other reactions the participation of peroxides is not so obvious (since no peroxides survive) but is commonly accepted as a primary feature of the reaction mechanism. A contrary view is, however, still sometimes expressed, and fairly recently Szent-Györgyi concluded that by the influence of a specific type of chemical catalyst the absorption of oxygen can lead directly, without intervention of peroxides, to the formation of olefin oxides (*Biochem. Z.*, 1924, **146**, 246).

The view that autoxidation occurring at olefinic centres leads first to the formation of cyclic peroxide groups, then to that of oxido-groups and later to glycols or products of chain scission, has often been expressed, although it could not be established as a *general* course of reaction in view of innumerable observations to the contrary. Ellis (*Biochem. J.*, 1936, **30**, 753) obtained yields of crystalline oxido-compounds as high as 15% from elaidic and oleic acids, as well as considerable yields of obviously chain-scission products. An alternative, however, to the cyclic peroxide–oxide–glycol–scission product sequence has been postulated by Willstätter and Sonnenfeld (*Ber.*, 1913, **46**, 2952), which seems to be accepted by most recent writers on the autoxidative changes occurring in vegetable oils (*e.g.*, Ellis, *J. Soc. Chem. Ind.*, 1926, **44**, 401T; Morrell and Marks, *J. Oil Colour Chem.*, 1927, **10**, 186; 1929, **12**, 183; Long and McCarter, *Ind. Eng. Chem.*, 1931, **23**, 786). This holds that the cyclic peroxide groups formed in the first stage of oxidation have the ability to isomerise to the corresponding unsaturated diol or its tautomeric ketol:

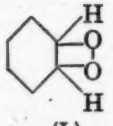


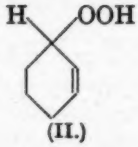
and would mean, if it were correct, that there is a direct and very simple path connecting the initia formation of a peroxide group with the final occurrence of chain scission at the original double bond, since the unsaturated enol might well be deemed to be susceptible to further oxidative attack culminating in scission. The hypothesis, however, fails completely to make any provision for the undoubted formation in some autoxidations of oxido-compounds and saturated 1 : 2-glycols, or indeed for the occurrence of secondary autoxidative change at all in peroxides derived from the substituted system ·CR:CR'· (R, R' = alkyl), since such peroxides would be structurally incapable of giving ketol tautomerides. It is the object of this and subsequent papers to examine various aspects of the autoxidation problem as it affects

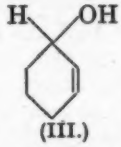
simple and high-molecular unconjugated * olefinic substances with a view to trace the main and subsidiary changes and to correlate these with certain other types of oxidative reaction to which olefinic substances are susceptible.

In 1928 Stephens (*J. Amer. Chem. Soc.*, **50**, 568) discovered that *cyclo*hexene, when treated with oxygen in daylight, gave a liquid peroxide, $C_6H_{10}O_2$, presumed to be a double-bond adduct (I), which could be isolated by distillation. In 1936 one of us (with E. S. Narracott), in the course of preliminary experiments on the oxidation of rubber, found that when commercial xylene was used as solvent and an organic cobalt salt as catalyst, the xylene underwent slow oxidation with production of tolualdehyde, *m*- and *p*-toluic acid, and an alcohol which was doubtless toluic alcohol (see Note, this vol., p. 185). This was one of a number of interesting examples, which it is hoped to discuss later elsewhere, of the strong reactivity of methylene groups situated in the α-position to olefinic double bonds—a reactivity involving replacement or separation of hydrogen atoms. On the assumption that the formation of a peroxide group is the first step in the oxidation by molecular oxygen, the primary oxidation product of xylene must have been a hydroperoxide, $CH_3{\cdot}C_6H_4{\cdot}CH_2{\cdot}OOH$, comparable with Rieche's monoalkyl peroxides, and it was of great significance, as reflecting the relative natural tendencies towards displacement of olefinic and methylenic hydrogen atoms in the system $\cdot CH{:}CH{\cdot}CH_2\cdot$ (at least in certain types of reactivity), that in xylene the usual aromatic replaceability of nuclear hydrogen is actually superseded by replaceability of α-methylenic hydrogen atoms. α-Methylenic reactivity, as distinct from ordinary double-bond additivity, appears indeed to be potentially important in the chemistry of most mono-olefinic and unconjugated polyolefinic compounds, and especially is this true of the latter, since in many of these, owing to the multiple unsaturation, the mobility of α-methylenic hydrogen seems to be enhanced.

Stephens's peroxide was re-examined by Hock (Hock and Schräder, *Naturwiss.*, 1936, **24**, 159; *Angew. Chem.*, 1936, **49**, 595; Hock, *Oel u. Kohle*, 1937, **13**, 697), who obtained certain interesting results as regards the reactivity of the peroxide (see below) but agreed with Stephens's formulation of the peroxide as the double-bond adduct (I). Our own examination of *cyclo*hexene peroxide, begun in 1939 with the object of throwing light on a number of perplexing observations made over several years of study of the autoxidation and general reactivity of rubber, was forestalled in an important respect by Criegee, Pilz, and Flygare (*Ber.*, 1939, **72**, 1799), who showed that the peroxide formed from *cyclo*hexene in ultra-violet light must be a hydroperoxide (II) still containing a double bond, since (1) it is reducible by sodium sulphite to *cyclo*hexen-3-ol (III), (2) it absorbs 1 mol. of bromine per mol., and (3) it contains one atom


(I.)


(II.)


(III.)

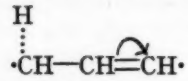
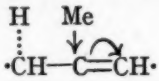
of active hydrogen per mol. This confirmed the above-mentioned indications of the importance of α-methylenic reactivity in the chemistry of olefinic systems and rendered desirable further investigation, especially of the secondary autoxidation processes, of *cyclo*hexene and other allied olefins.

Point of Oxidative Attack.

In numerous oxidations of carefully purified *cyclo*hexene, carried out by us in quartz flasks in the radiation from a mercury-vapour lamp, there was usually formed in 2—4 hours at temperatures between 30° and 40° about 30—40% of oxygenated material containing about 80% of monomeric peroxide, as determined both by direct estimation of peroxidic oxygen and by isolation of the pure peroxide by fractional distillation at greatly reduced pressure. The peroxide thus isolated behaved exactly as described by Criegee in regard to unsaturation, active hydrogen content, and reducibility to *cyclo*hexenol, and also was quantitatively reducible by hydrogen and platinum to crystallisable *cyclo*hexanol, and not to *cyclo*hexane-1 : 2-diol. Hence, peroxide formation in itself involved none of the reduction of unsaturation which must result from any addition of oxygen to the original double bond : on the contrary, oxidative attack was here confirmed to affect in the primary reaction only the α-methylene groups. The mode of attack, involving displacement of a methylenic hydrogen atom, is doubtless similar to that occurring in the peroxidation of saturated hydrocarbons, although the process is enormously facilitated in olefinic substances by an enhanced tendency to dissociation of hydrogen promoted apparently (in spite of the fact that the dissociation is probably of free-radical rather than of ionic character) by normal electronic dis-

* Owing to the difference in structure between conjugated and unconjugated olefins, the course of autoxidative reaction in the two cases must necessarily differ considerably, although certain features will be similar.

placements in the double-bonded system (IV); furthermore the attack is found to be accelerated, as might perhaps be expected, if an inductively-acting alkyl group is attached to the ethylenic carbon atom adjacent to the methylene group (system V), as occurring in trimethylethylene or 1-methyl*cyclo*hexene. In the

(IV.)  (V.) 

general case, therefore, although any α-methylene group is a potential reactive centre, the most likely point of attack where several such groups are present may be expected to be that one in which the tendency to dissociation of hydrogen will be most facilitated by normal electronic polarisation. Hence, although attack is possible at either of the methylene groups in the unsubstituted system $\cdot CH_2 \cdot CH{:}CH \cdot CH_2 \cdot$, it is most likely to occur to the greatest extent at the points distinguished by asterisks in the systems (VI—X):*

(VI.) $\cdot \overset{*}{C}H_2 \cdot CMe{:}CH \cdot CH_2 \cdot$ $\cdot \overset{*}{C}H_2 \cdot CMe{:}CH \cdot CH_2 \cdot CH_2 \cdot \overset{*}{C}H_2 \cdot CMe{:}CH \cdot CH_2 \cdot$ (VII.)

$CH_3 \cdot \overset{*}{C}H_2 \cdot CH{:}CH \cdot CH_3$ (VIII.) $\overset{*}{C}H_3 \cdot CMe{:}CH \cdot CH_2 \cdot CH_3$ (IX.) $CH_3 \cdot \overset{*}{C}H_2 \cdot CMe{:}CH \cdot CH_2 \cdot CH_3$ (X.)

Peroxide Decomposition.—Organic peroxides have very different degrees of stability as is well seen in their widely-varied ease of reduction and their stability at room temperature. It is well attested that the secondary reactions following on the initial formation of peroxide groups commonly involve some loss of unsaturation, and a review of numerous published observations makes it clear that the rapidity of this loss varies with the character (stability or reactivity) of the peroxidic substances formed, and with the experimental conditions. Both of these factors affecting the ease of peroxide decay are very important. In the case of *cyclo*hexene, as seen above, a few hours' autoxidation under the most favourable conditions gives oxygenated material which contains much pure hydroperoxide, but even so the original olefinic unsaturation of the hydrocarbon (per molecule) does not survive in the product wholly undiminished. The same holds good in the case of two other autoxidations which we have studied, *viz.*, those of 1-methyl- and 1 : 2-dimethyl-*cyclo*hexene. If, however, in these examples the temperature during oxidation is allowed to rise above 40°, or the peroxide is formed so slowly (*e.g.*, without catalysis by light or other agency) that the oxidation process is unduly prolonged (*e.g.*, for many days), the yield of pure peroxide becomes much diminished and that of secondary products correspondingly increased. Other substances are similar to *cyclo*hexenes in this respect. Rubber when oxidised rapidly in solution under good illumination at *ca.* 15° incorporates 80% of the oxygen in peroxide form during the early stages of reaction, although later this high yield decreases; but if the oxidation is conducted under less favourable conditions no high percentage of the oxygen intake survives as peroxide at any stage, and in commercial processes, where an organic cobalt salt is used as catalyst and the temperature is allowed to rise unchecked, only traces of peroxide survive. With autoxidised linseed oil many previous observations indicate that the peroxide-content rises during the first few hours to a maximum which represents only a fraction of the total oxygen intake (25—40%, according to the experimental conditions), and afterwards slowly decreases: at the same time the unsaturation decreases.

The fact that the increase in the oxygen uptake (with concomitant formation of peroxidic matter) is accompanied by a decrease in the unsaturation of the material has usually been interpreted to mean that oxygen adds directly in peroxide form at the double bonds, although the gross inexactitude of the quantitative relationship between the two has been a continual source of perplexity. Scrutiny of the wealth of recorded data on autoxidative changes leaves little doubt but that the diminution in unsaturation, whether this is slow or rapid, is partly a matter of the experimental conditions. This is understandable if the primary reaction (*i.e.*, the absorption of oxygen to form peroxide groups) is recognised to consist quite generally in the formation of hydroperoxide groups on the α-methylenic carbon atoms, for then the actual oxygen absorption does not affect at all the unsaturation of the system: only later, when the secondary reactions brought into being by the decay of peroxide groups begin, does the unsaturation become affected, and the prevailing conditions of reaction are likely to influence materially the speed of decay and hence the length of life of the peroxide groups and probably to affect the mode of their decomposition. The secondary

* This expectation is most completely fulfilled in the analogous attack on the α-methylene groups of olefins by selenium dioxide in the presence of acetic acid. Here, acetoxy-groups become substituted in the following systems at the points marked by asterisks (Guillemonat, *Ann. Chim.*, 1939, **11**, 143): $\overset{*}{C}H_3 \cdot CMe{:}CHMe$, $CH_2 \cdot \overset{*}{C}H_2 \cdot CMe{:}CH_2$, $\overset{*}{C}H_2 \cdot CPr^{\beta}{:}CHMe$, $\overset{*}{C}H_3 \cdot CMe{:}CHEt$, $CH_2 \cdot \overset{*}{C}H_2 \cdot CPh{:}CHMe$, $CH_2 \cdot \overset{*}{C}H_2 \cdot CH{:}CHMe$, $\overset{*}{C}H_2R \cdot CEt{:}CH \cdot CH_2R$, $CHMeR \cdot CH{:}CH \cdot \overset{*}{C}H_2R$. The similarity of selenium dioxide oxidation to peroxidation is remarkable.

reactions tend almost entirely towards saturation of the olefinic centres (unless conditions which promote dehydration of the secondary products are employed), and hence the ultimate autoxidation products will often contain but little peroxide and be almost saturated: the actual peroxide content and the condition of unsaturation at intermediate points will depend mainly on the respective rates of formation and decomposition of the peroxide. What these reactions are, and the way in which their course and progress are affected by the experimental conditions, is shown in part below.

As noted by Criegee, the peroxide of *cyclo*hexene which is formed in a few hours under good illumination at about 30° is much purer than Hock's original product, formed during a long period (200 hours) in diffused light. But even the best products, in spite of being distilled expeditiously at pressures below 1 mm. (bath temperature below 80°), give a small peroxide fraction, of rather low peroxide content and slightly high boiling point, in which some degree of secondary change has occurred; any elaborate fractionation of the peroxide unless by molecular distillation at low temperatures serves only to increase this fraction. We have found also that even under the most favourable conditions of operation the oxidation product does not consist of unchanged *cyclo*hexene and the hydroperoxide fraction only. Careful fractionation of the *lower-boiling portion* of the product at reduced pressure always gives some *cyclo*hexene oxide and some *cyclo*hexenol in addition to the unchanged *cyclo*hexene; and if this fractionation is conducted at atmospheric pressure, some of the *cyclo*hexenol is dehydrated, and the water so liberated hydrates a part of the *cyclo*hexene oxide to *trans-cyclo*hexanediol, m. p. 104°. That the oxide and *cyclo*hexenol are formed during the oxidation, and not subsequently, can be demonstrated by reducing the oxidation product with sodium sulphite immediately the oxygen intake ceases, and then fractionating the peroxide-free mixture. It is difficult to envisage any likely means of formation of the simple olefin oxide (*e.g.*, by the hydrolysis or reduction of, or by the loss of free oxygen from, the peroxide) under the conditions of reaction employed other than the direct oxidation of *cyclo*hexene by the *cyclo*hexene peroxide. This would be analogous to the oxidation of olefins to oxido-derivatives by peracids such as perbenzoic acid, and might be represented as being initiated by the occurrence of co-ordination between a polarised ethylenic carbon and a peroxidic oxygen atom, and completed by the elimination of a molecule of alcohol (*cyclo*hexenol) from the co-ordination complex:

$$\cdot CH{:}CH\cdot + R\cdot OOH \longrightarrow \cdot \overset{-}{C}H\cdot CH\cdot \longrightarrow \cdot CH\cdot CH\cdot + R\cdot OH \quad . \; . \; . \; . \; (A)$$
$$\qquad\qquad\qquad\qquad\quad | \qquad\quad \diagdown\diagup$$
$$\qquad\qquad\qquad\quad HO\cdot OR \qquad O$$
$$\qquad\qquad\qquad\quad \overset{+}{}$$

It is important to note that the formation of *cyclo*hexene oxide in this way must necessarily involve a bimolecular reaction, and it was of interest to discover whether, by heating together the suggested reactants, *cyclo*hexene oxide is produced. Tests of this kind carried out at 100° gave *cyclo*hexene oxide in small yield, together with *cyclo*hexenol * and some polymeric material. It is readily understood why no large yield of oxido-compound is formed, since the latter is likely to react at 100° (especially in the presence of small amounts of acid) † with the hydroxylic materials present. The rapid autoxidation of 1-methyl- and of 1 : 2-dimethyl-*cyclo*hexene at 30—40° in ultra-violet light was also found to give rise to the corresponding oxides (1-methyl- and 1 : 2-dimethyl-*cyclo*hexene 1 : 2-epoxide) and alcohols (1-methyl-*cyclo*hexenol and 1 : 2-*dimethyl*cyclo*hexen*-3-*ol*), in about equal amounts, as well as to a good yield of the parent *hydroperoxides*; here, however, the low-boiling decomposition products were produced in rather larger yield. The oxides gave on hydrolysis with water at 110°, or better with dilute sulphuric acid, the high-melting forms (respectively) of 1-methyl- and 1 : 2-dimethyl-*cyclo*hexane-1 : 2-diol. The alcohol from the peroxide of 1-methyl*cyclo*hexene proved to be a mixture of the 6- and the 3-hydroxy-compound, the former preponderating, so that the peroxide, in conformity with the views on the point of oxidative attack expressed above, contained both the 6- and the 3-hydroperoxide. This fact received confirmation in several ways.

Ketone Formation.—As seen above, one of the decomposition products of *cyclo*hexene hydroperoxide is *cyclo*hexene-3-ol, and it is a striking fact, noted by Schmidt (*Ber.*, 1930, **63**, 1139), that in various autoxidations of cyclic olefins described in the literature similar unsaturated alcohols have almost invariably been obtained. A review of the examples shows that the hydroxy-group is attached to that one of the ring carbon atoms at which in our view hydroperoxidation would be most likely to occur, except that in the case of α-pinene, in which the system $\cdot CH_2\cdot CH{:}CMe\cdot CH\langle^{C}_{C}$ occurs, attack at both (alternatively) of the

* It is difficult in experiments of this kind to demonstrate with certainty that the *cyclo*hexene oxide and *cyclo*hexenol are formed in molecularly equivalent amounts.

† Some proportion of organic acid formed by chain scission is likely to appear as reaction proceeds, or more rapidly at the temperature of distillation.

α-carbon atoms has been observed. These autoxidations have been carried out at 70° or above, or for long periods at a lower temperature, usually in presence of a catalyst. In many of the examples (*e.g.*, see Table I) the alcohol is accompanied by the corresponding ketone, and it seems at first sight not unlikely

TABLE I.

Olefin.	Catalyst.	Temp.	Time.	Ketone.	Authors.
*cyclo*Hexene	Os (colloidal)	?	22 hours	*cyclo*Hexan-1-ol-2-one	Willstätter and Sonnenfeld [1]
1-Methyl*cyclo*hexene	None	95°	?	1-Methyl*cyclo*hexen-6-one	Dupont [2]
,,	Fe phthalocyanine	70°	72 hours	,,	Cook [3]
1 : 2-Dimethyl-*cyclo*hexene	None	70°	1 week	1 : 2-Dimethyl*cyclo*hexen-3-one	Dupont [4]
α-Pinene	None (iron vessel)	Room temp.	6 months	Verbenone	Blumann and Zeitschel [5]
,,	Fe phthalocyanine	70°	4 days	,,	Cook [3]
,,	Os; sunlight	?	?	,,	Wienhaus and Schumm [6]
β-Pinene	Co resinate	*ca.* 30°	88 hours	Pinocarvone	Schmidt [7]
Limonene	None	Room temp.	2½ months	Carvone	Blumann and Zeitschel [8]
Tetralin	Fe phthalocyanine	70°	12 hours	α-Tetralone	Cook [3]

[1] *Ber.*, 1913, **46**, 2952; 1914, **47**, 2814. [2] *Bull. Soc. chim. Belg.*, 1936, **45**, 57. [3] J., 1938, 1778. [4] *Bull. Soc. chim. Belg.*, 1936, **46**, 21. [5] *Ber.*, 1913, **46**, 1178. [6] *Annalen*, 1924, **439**, 20. [7] *Loc. cit.* [8] *Ber.*, 1914, **47**, 2623.

(especially in view of the fact that water is almost invariably formed in olefinic autoxidations) that a direct dehydration of the olefinic hydroperoxide to form a ketone may have occurred:

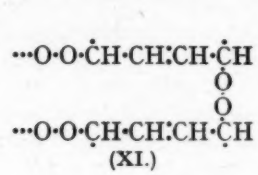
$$\cdot\underset{\underset{OOH}{|}}{C}H\cdot CH{:}CH\cdot \longrightarrow \cdot\underset{\underset{O}{\|}}{C}\cdot CH{:}CH\cdot + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

But in none of our autoxidation experiments at 30—40° with *cyclo*hexene or the more rapidly autoxidisable 1-methyl- and 1 : 2-dimethyl-*cyclo*hexene has any recognisable amount of cyclic ketone been formed, although water is a product of reaction. Also, it is plain that to the extent that a hydroperoxide, R·OOH, undergoes dehydration, to that extent it relinquishes its oxidative habit, which much evidence shows to be the principal reactive tendency; furthermore, there is little in the literature to indicate that alkyl peroxides may be able to undergo dehydration, unless the ordinary decomposition of hydrogen peroxide to water and oxygen is accepted as an indication. Nevertheless, both Cook (*loc. cit.*) and Dupont (*Bull. Soc. chim. Belg.*, 1936, **45**, 57) have reported the formation in diffused light at 70° and 90°, respectively, of a cyclic ketone from 1-methyl*cyclo*hexene,* the former author using an active iron catalyst and the latter none at all. It is clear that, whereas the alcohol appears to be a necessary primary decomposition product of the peroxide, the ketone does not; also it appears that for the production of the ketone in appreciable amount either a higher temperature than 40° is required, or some other condition (probably one involving the activity of the catalyst) needs to be fulfilled. We have not succeeded in directly oxidising *cyclo*hexen-3-ol to the corresponding ketone by exposing it to oxygen in ultra-violet light at 30—40°, neither the oxygen nor the organic peroxides which are readily formed from the alcohol under these conditions having apparently the necessary oxidative power. This suggested (although it in no way proved) that the ketone is formed directly from the peroxide, rather than indirectly *via* the alcohol. Hence it seemed most reasonable to look for the origin of the ketone in the isomerising capacity or in one of the paths of direct decomposition of the hydroperoxides.

Ketone Formation by Isomerisation of the Peroxides or Oxides.—The autoxidation of conjugated diolefins appears to yield either polymolecular peroxides in which the diene units are terminally linked as in (XI) (Bodendorff, *Arch. Pharm.*, 1933, **271**, 1) or unimolecular ones such as ascaridol (terpinene peroxide) and the peroxides of 2 : 4-cholestadiene, ergosterol, dehydroergosterol, rubrene, naphthacene, pentacene, anthracene, etc. In all of these unimolecular examples the existing evidence leaves little doubt as to the formation of the peroxides by the transannular addition of oxygen at the ends of conjugated diene systems

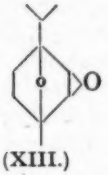
* Cook called the ketone 1-methyl*cyclo*hexen-3-one and the cyclic alcohol 1-methyl*cyclo*hexen-3-ol, whereas Dupont considered his ketone and alcohol to be 1-methyl*cyclo*hexen-6-one and 1-methyl*cyclo*hexen-6-ol respectively. As indicated above, owing to the formation in the original oxidation of two isomeric forms of the hydroperoxide, both the 6- and the 3-alcohol could hardly fail to be present in Cook's and Dupont's preparations; and if the ketone is formed directly from the alcohol or from the parent peroxide, then both the 6- and the 3-ketone would also be present (see below).

(for review of evidence, see Bergmann and McLean, *Chem. Rev.*, 1941, **28**, 367). Now in the case of ascaridol (XII) it has been shown that the transannular peroxide passes on heating at 150° into the oxide (XIII), whilst the peroxide formed from 2 : 4-cholestadiene under mild illumination isomerises (in alcohol solution) on exposure to sunlight to give a saturated ketone. The same ketone is formed directly from the cholestadiene if oxygenation takes place in sunlight, and Skau and Bergmann (*J. Org. Chem.*,



(XI.)

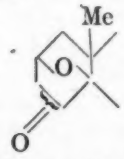
(XII.)



(XIII.)

(XIV.)

(XV.)



(XVI.)

1939, **3**, 66) suggest that the peroxide (XIV) isomerises first to the oxide (XV), which immediately rearranges to give the ketone (XVI); the location of the carbonyl group, however, at position 3 or 4 in (XVI) has not yet been precisely determined. Ergosterol peroxide can also be converted into an epoxide-ketone, but in this case by heating at 185—190° (Windaus, Bergmann, and Luttringhaus, *Annalen*, 1929, **472**, 195; see also Skau and Bergmann, *loc. cit.*); the ketone group has not been shown to appear in the bridged ring, and indeed it may well occur at an original centre of unsaturation in the side chain (Bergmann and McLean, *loc. cit.*, p. 377).

Amongst recorded investigations of the autoxidation of unconjugated olefinic substances there is, so far as we are aware, no clear instance where direct isomerisation of peroxide to ketone (similar to the foregoing examples in the conjugated series) has been demonstrated. The analogous change in the unconjugated olefin series to that represented by the transformation (XIV) ⟶ (XV) ⟶ (XVI) would be:

$$>C(OOH)\cdot CH{:}CH\cdot \longrightarrow >C(OH)\cdot \underset{\underset{O}{\vee}}{CH\cdot CH}\cdot \longrightarrow >C(OH)\cdot CO\cdot CH_2\cdot \text{ or } >C(OH)\cdot CH_2\cdot CO\cdot$$

Morrell and his collaborators (*loc. cit.*; also *J. Soc. Chem. Ind.*, 1931, **50**, 27T; 1936, **55**, 237T; 1939, **58**, 159T; *J. Oil Colour Chem.*, 1940, **23**, 103) have claimed that enolisable α-ketols are normally formed in the case of autoxidised drying-oil acids or glycerides in the manner: $\overset{\cdot CH\cdot CH\cdot}{\underset{O-O}{|\quad|}} \longrightarrow \overset{\cdot CH\cdot CO\cdot}{\underset{OH}{|\quad|}}$, but we can find no justification of the claim in any of the experimental evidence which these authors advance; and indeed, the measurement of ketol content in terms of carbonyl and active hydrogen content by these and other authors (cf. Bolam and Sim, *J. Soc. Chem. Ind.*, 1941, **60**, 507) is necessarily rendered invalid by the fact that the peroxide groups present are highly oxidative, hydroxylic ·OOH groups, and not the less reactive, non-hydroxylic ·O·O· groups assumed by them. In numerous autoxidations of *cyclo*hexene and 1-methyl*cyclo*hexene we have found none of the easily recognisable α-ketol among the oxidation products, although Willstätter and Sonnenfeld (*loc. cit.*), as noted above, obtained some α-ketol (*cyclo*hexan-1-ol-2-one) under their conditions of autoxidation. In view, however, of the frequent formation of α-ketols as intermediates during the oxidative scission of double bonds (*e.g.*, by permanganate) this product seems most likely to have been derived by the further oxidation of the corresponding epoxide or saturated 1 : 2-diol. At present, therefore, the occurrence of a substantial degree of ketone formation by an isomerisation of peroxide groups analogous to that reported for conjugated compounds seems doubtful, but it is hoped to publish further observations on this point later.

Ketone Formation by Peroxide Decomposition.—Various authors have referred to the dual rôle of autoxidation catalysts in promoting both peroxidation and the subsequent decomposition of the peroxides, although the balance between formation and decomposition does not appear to have been studied. Cook (*loc. cit.*) obtained methyl *cyclo*hexenone by autoxidation of methyl*cyclo*hexene at 70°, using ferrous phthalocyanine as catalyst, but in our experiments no significant amount of ketone was formed by oxidation in ultra-violet light at *ca.* 35°. We have therefore tested the ketone-forming action of Cook's catalyst on pure methyl*cyclo*hexene hydroperoxide, and found that this catalyst promotes a very energetic decomposition of the peroxide to cyclic alcohol, cyclic ketone, and other products, the ketone being in substantial

yield and consisting of two isomeric compounds, 1-methyl*cyclo*hexen-6- and -3-one. Of these isomerides the former preponderated, so it is fairly certain that they are derived directly from the corresponding alcohols or the parent hydroperoxides. In the case of *cyclo*hexene hydroperoxide ferrous phthalocyanine caused similar energetic decomposition with formation of much *cyclo*hexenol, a substantial yield of ketone, a little *cyclo*pentene-1-aldehyde, and other products. The ketone was *cyclo*hexene-3-one, and the aldehyde a scission product formed by causes discussed later. Similarly, decomposition of 1 : 2-dimethyl*cyclo*hexene hydroperoxide gave a substantial yield of 1 : 2-dimethyl*cyclo*hexen-3-one, together with the related cyclic alcohol and other products. The ketone was contaminated with a little of a second ketone which appeared to be the ring-scission product, 1 . 4-diacetylbutane.

As regards the identity of the immediate precursor of the ketonic products (hydroperoxide or alcohol) in these catalytic decompositions, the evidence is not yet clear. Water is always eliminated in the decompositions, as though by dehydration of the hydroperoxide (equation B), but so it is in autoxidations in which no ketonic product is formed. The normal decomposition product of the peroxide always appears to be the cyclic alcohol, and to permit the formation of this substance the potential oxidising power of the active peroxide groups must be dissipated. This oxidising capacity is largely utilised in oxidative attack, culminating in chain scission, at the unsaturated centres, but it may well be that in the presence of an active catalyst it is sufficiently energetic to bring about the oxidation of the cyclic alcohol to the corresponding ketone. A crucial test on this point remains to be applied. It is of interest, however, to note that the ketones formed in this way by catalytically-promoted peroxide decomposition, unlike those which would be formed by peroxide isomerisation, are unsaturated, whereas the trend of autoxidation in vegetable oils seems, according to published observations, to be towards the production of complete saturation. Possibly the formation of unsaturated ketones is mainly a special characteristic of hydroaromatic autoxidations.

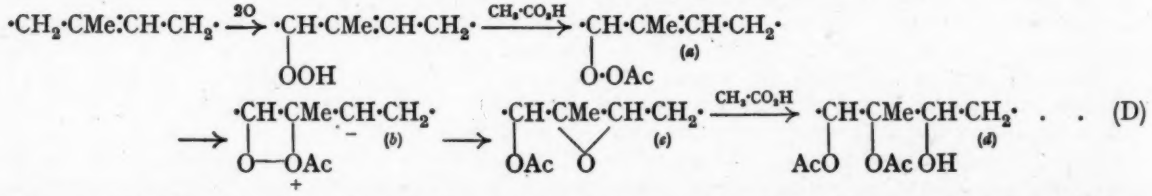
Vigorous decomposition of *cyclo*hexene hydroperoxide occurs when it is heated to about 120° in an open vessel. The reaction is probably similar to that promoted by ferrous phthalocyanine, but the products have not been closely examined.

Oxidative Action of Hydroperoxides in the Presence of Acids.—One of us, with Bloomfield (*J. Soc. Chem. Ind.*, 1935, **54**, 2T), observed that the oxidation of rubber when carried out in presence of a cobalt catalyst is greatly accelerated if a little acetic anhydride is added; moreover, the action of the acetic anhydride is not simply catalytic, since the oxidation products are extensively acetylated. Later, one of us noticed that when small lumps of rubber are refluxed for a day with acetic anhydride, little save slight swelling of the rubber ensues, but when the anhydride is refluxed rapidly over the rubber in an open extraction tube, the hydrocarbon undergoes rapid and advanced degradation in which atmospheric oxidation is the principal factor. The influence of acids does not appear to be confined to organic acids, since attempts to hydrate dihydromyrcene, $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_3$, by refluxing it with sulphuric acid in an open vessel (with a little silver sulphate as hydration catalyst) gave oxidation products instead of hydration products. On the other hand, alkali has no marked promoting action on the autoxidation of rubber, although pyridine appears to assist reaction.

The reactive hydroperoxides which are formed under nearly anhydrous conditions by the action of oxygen on olefins would be expected to react immediately with organic acids to give alphyl esters of the corresponding peracids,

$$R{\cdot}OOH + R'{\cdot}CO_2H \longrightarrow R'{\cdot}C(OH)_2{\cdot}OOR \longrightarrow R'{\cdot}CO{\cdot}OOR + H_2O \quad . \; . \; . \quad (C)$$

which in turn would behave like free peracids in their additivity to olefinic centres:

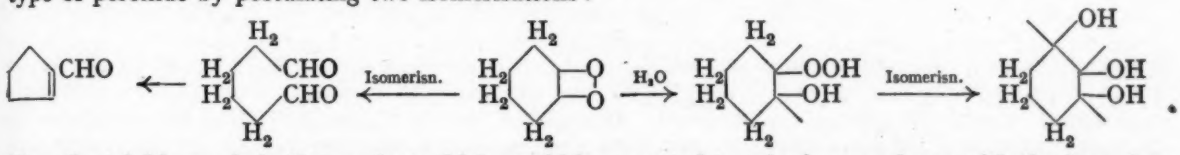


(D)

The epoxide shown in stage (*c*) probably never appears as an isolable compound; also the addition of acetic acid at the epoxy-group (change $c \longrightarrow d$), and of ·OAc at the double bond (change $a \longrightarrow b$), may take place in the reverse direction to that shown in scheme (D). The reaction in presence of an acid anhydride would be precisely analogous, yielding eventually for pure acetic anhydride (free from acetic acid) triacetoxy-derivatives, $\cdot CH(OAc){\cdot}CMe(OAc){\cdot}CH(OAc){\cdot}CH_2\cdot$; but with either the free fatty acid or the anhydride further oxidative attack might lead to scission between either pair of oxygenated carbon

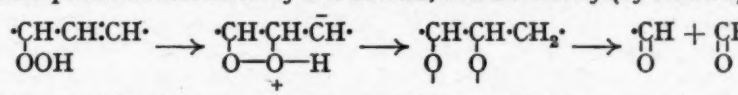
atoms, although this probably would not occur nearly so readily with esterified polyalcohols as with the corresponding free alcohols. The satisfactory confirmation of such a course of reaction in the case of rubber has only recently become possible by the development in connexion with this work of a precision method for the determination of active hydrogen in high-molecular substances (Bolland, *Trans. Inst. Rubber Ind.*, 1941, **16**, 267). The details of this confirmation form the subject of Part III.

Whether or no in the above-cited oxidation of dihydromyrcene in presence of dilute sulphuric acid there is slow and transient formation of peracid (? permonosulphuric acid), there is certainly engendered a vigorous peroxidic oxidising capacity when pure *cyclo*hexene- and alkyl*cyclo*hexene-hydroperoxides are mixed with dilute sulphuric acid. Hock (*Oel u. Kohle, loc. cit.*) observed that *cyclo*hexene peroxide, when allowed to stand with sulphuric acid at 35—40°, gave mainly *cyclo*pentenealdehyde (*ca.* 20% yield) and *cyclo*hexane-1 : 2 : 3-triol (50% yield),* and he sought to explain their formation from a supposed cyclic type of peroxide by postulating two isomerisations:



Now the triol is precisely the product which would be expected to arise in accordance with the foregoing schemes (C) and (D) if an aqueous mineral acid were substituted for the organic acid or anhydride, but the formation of *cyclo*pentenealdehyde (*i.e.*, the dehydrated aldol from adipic dialdehyde) is more difficult to formulate, since the oxygeno-substituent has apparently disappeared from the α-carbon atom. It seemed possible at first that the parent adipic dialdehyde might have arisen by the action of the hydroperoxide, and subsequently perhaps of peracid, on residual *cyclo*hexene in the peroxide employed (Equation A), but many repetitions of Hock's experiment with peroxide which had been entirely freed from *cyclo*hexene have always given some *cyclo*pentenealdehyde together with a little *cyclo*hexenol, although the main products were *cyclo*hexanetriol and a " dimeric " acidic residue; moreover, we have found that by heating the peroxide with water at 110° the same four products are formed but in different proportions. Hence, in order to account for the formation of *cyclo*pentenealdehyde, it is necessary either to envisage a reaction, inter- or intra-molecular in kind, in which the peroxide group acts oxidatively at the double bond and simultaneously disappears entirely from the α-methylene group, or alternatively to look for the source of the *cyclo*pentenealdehyde in the incomplete homogeneity of the hydroperoxide used.

Now it is uncertain whether the changes expressed in equations (A) and (D), or indeed the peroxide→oxide→ketone-conversion of the above-mentioned trans-annular peroxides, are necessarily always intramolecular ones, but the transformation of pure *cyclo*hexene hydroperoxide into adipic dialdehyde by the action of dilute sulphuric acid must necessarily be intramolecular, since otherwise the formation of α-hydroxyadipic dialdehyde would be inescapable. A conceivable course of reaction is the following, in which co-ordination of an ethylenic carbon atom with a peroxidic oxygen atom gives an oxonium complex, which on disruption produces momentarily a di-radical, and ultimately (by scission) two aldehyde groups:



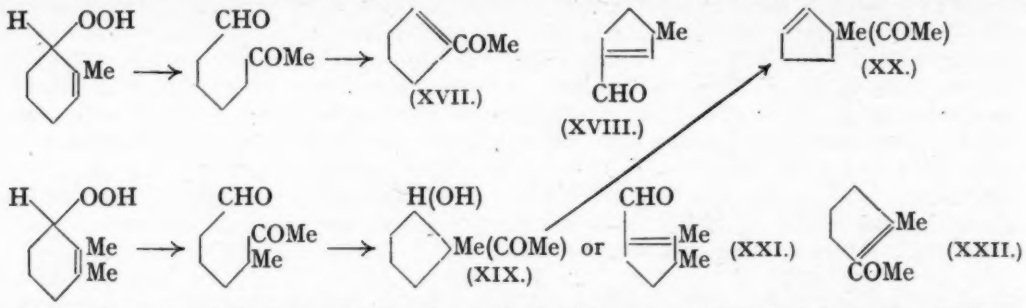
(E)

By this mechanism scission of the *cyclo*hexene could occur without loss of any carbon atoms at a single bond adjacent to the original double bond, and adipic dialdehyde could thus be formed. But if this course of reaction were correct, 1-methyl*cyclo*hexene 6-hydroperoxide would be expected to give with sulphuric acid 1-acetyl*cyclo*pentene (XVII), and the isomeric 3-hydroperoxide similarly to give the aldehyde (XVIII). Likewise 1 : 2-dimethyl*cyclo*hexene 3-hydroperoxide should give either 1-acetyl-1-methyl*cyclo*penten-2-ol (XIX) [leading possibly to its dehydration product 1-acetyl-1-methyl*cyclo*pentene (XX)] or 2 : 3-dimethyl*cyclo*penten-1-aldehyde (XXI).

We have found that the normally-formed mixture of 1-methyl*cyclo*hexene 6- and 3-hydroperoxides does indeed give 1-acetyl*cyclo*pentene (nearly 5% yield), together with 1-methyl*cyclo*hexanetriol (40—50% yield) and a little methyl*cyclo*hexenol, but no aldehyde or second carbonyl compound is formed; also 1 : 2-dimethyl*cyclo*hexene 3-hydroperoxide gives quite analogously a mixture of a ketone, $C_8H_{12}O$, much 1 : 2-*dimethyl*cyclo*hexane*-?1 : 2 : 3-*triol*, and a little 1 : 2-dimethyl*cyclo*hexen-3-ol. The ketone $C_8H_{12}O$, however, is found to be, not (XX), but the well-known acetylmethyl*cyclo*pentene (XXII) which would

* In his first communication Hock (*Naturwiss.*, 1936, **24**, 159) announced the formation of a 50% yield of *cyclo*hexane-1 : 2-diol, m. p. 104°, but subsequently claimed high yields of the triol. In our repetitions of Hock's experiments we have always obtained the triol, but never the diol.

result *via* 1 : 4-diacetylbutane from fission of the *cyclo*hexene ring at the double bond; moreover, the crude ketone contains a little 1 : 4-diacetylbutane. The formation of only the one observed cyclic carbonyl



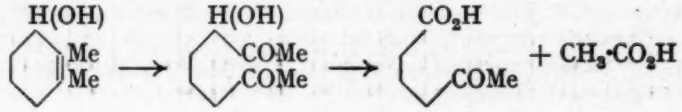
compound from the isomeric hydroperoxides of 1-methyl*cyclo*hexene, and that of the ketone (XXII) from the hydroperoxide of 1 : 2-dimethyl*cyclo*hexene, shows quite clearly that primary fission of the *cyclo*hexene ring occurs only at the original double bond. It must be concluded, therefore, that the formation of *cyclo*pentenealdehyde, of acetyl*cyclo*pentene, and of acetylmethyl*cyclo*pentene from the hydroperoxides of *cyclo*hexene, methyl*cyclo*hexene, and dimethyl*cyclo*hexene, respectively, is due to the presence of some secondary oxidation product in even the best specimens of hydroperoxide obtained.

Special tests with *cyclo*hexene hydroperoxide and methyl*cyclo*hexene hydroperoxide showed that the proportion of *cyclo*pentenealdehyde or acetyl*cyclo*pentene formed increased very markedly (up to 10% yield) when slightly high-boiling specimens of hydroperoxide of more or less low peroxidic oxygen content were treated with sulphuric acid; but no single specimen of hydroperoxide prepared by our usual procedure (rapid oxidation of the hydrocarbon followed by two distillations with the distillation-bath below 80°), even although it showed a correct peroxidic oxygen content, gave a sulphuric acid reaction product which was entirely free from the by-products in question. The discrepancy concerning the peroxide content is easily explicable, since the best method of determination available (see p. 133) is liable to an error of $\pm$ 5% of the true value; it seems clear, therefore, that some more rigorous procedure than the one adopted would be necessary in order to prepare the hydroperoxides entirely free from their secondary decomposition products.

The impurity is probably the saturated diol derived from *cyclo*hexene *via* the epoxide (equation A), and indeed, very small yields of this substance have been isolated on several occasions from the " dimeric " residue left after distillation of the peroxide (see below).

Oxidative Action of Hydroperoxides in the Presence of Alkali.—Hock and Gänicke (*Ber.*, 1938, **71**, 1430) found that when *cyclo*hexene peroxide is shaken with dilute sodium hydroxide solution at a temperature not above 30°, much *cyclo*hexenol is formed, together with a mixture of acids comprising α-hydroxyadipic and adipic acids, as well as small amounts of glutaric acid and volatile fatty acids which are doubtless formed by further oxidation of hydroxyadipic acid. *cyclo*Hexen-6-ol is the normal hydrolysis product of the hydroperoxide ($R{\cdot}OOH + H{\cdot}OH \longrightarrow R{\cdot}OH + H_2O_2$) and we have obtained yields of this alcohol up to 80% of the theoretical. α-Hydroxyadipic acid, formed by the oxidative action of liberated hydrogen peroxide (or possibly to some extent of *cyclo*hexene hydroperoxide) on *cyclo*hexenol or *cyclo*hexene hydroperoxide, is also to be expected, and Hock has shown that this is the principal acidic product (40% of total acids; overall yield, 7·8%). The formation, however, of adipic acid (9% of the total acids in Hock's experiments; overall yield, 1·9%), which we have qualitatively verified, requires explanation, since if the acid is formed from *cyclo*hexene 6-hydroperoxide the α-carbon atom must in this case also have become in some unusual way deoxygenated. We have no doubt that the source of the acid, like that of the *cyclo*pentenealdehyde formed by the action of water, sulphuric acid, heat, or a decomposition catalyst (see below) on the peroxide, is the same non-peroxidic impurity contained in the peroxide used which was referred to above. The 1 : 2-diol would be likely to undergo ready attack by hydrogen peroxide or alkyl hydroperoxide in alkaline solution.

1 : 2-Dimethyl*cyclo*hexene 3-hydroperoxide gave with alkali much 1 : 2-dimethyl*cyclo*hexen-3-ol, together with the expected oxidation products, γ-acetylbutyric and acetic acids. There was formed also in very small yield a high-melting, water-soluble acid (m. p. 196—197°).



1-Methyl*cyclo*hexene hydroperoxide gave analogously much methyl*cyclo*hexenol and a mixture of several other products, including (*a*) a little γ-acetylbutyric acid derived from the 3-substituted component of the hydroperoxide mixture, (*b*) a high-melting, water-soluble *acid*, $C_7H_{10}O_2$ (m. p. 207°) very similar to the one from dimethyl*cyclo*hexene hydroperoxide, which remained unreduced on treatment with hydrogen and platinum but was readily oxidised by permanganate to a highly oxygenated acid (? $C_7H_{10}O_6$) of m. p. 69°, and (*c*) a syrupy mixture of acids doubtless containing the oxidative scission products of the 6-hydroperoxide. The high-melting acid, $C_7H_{10}O_2$, was not certainly identified but probably retained the *cyclo*hexane ring intact. Much of the oxidative action promoted by the action of alkali is probably due to the hydrogen peroxide formed by hydrolysis of the hydroperoxides.

Formation of Dimeric Products.—Stephens (*loc. cit.*) reported that when *cyclo*hexene peroxide was isolated by fractional distillation there remained behind a considerable liquid residue which, from its empirical composition and molecular weight, he concluded to be a dimeride of the peroxide containing one peroxide group and probably one active hydrogen atom (Found : 0·68 atom) per molecule. We have analysed a number of these residues from *cyclo*hexene and methyl*cyclo*hexene hydroperoxides, and found them to have approximately the characteristics described by Stephens. The amounts of residues formed in our experiments depended largely on the duration of heating during fractionation, or of exposure to ultra-violet light during the oxidation. New quantities of high-boiling residue were certainly formed at each distillation of the peroxide, but a good deal of the residue ordinarily isolated from oxidation products seemed to be formed during the original oxidation. Irradiation of the isolated hydroperoxide in a nitrogen atmosphere gave viscous yellow polymeric residues.

Now, the intermolecular additions which occur during the autoxidation of these simple unsaturated hydrocarbons are widely encountered in the autoxidation of other olefinic substances and are specially important in the case of the drying oils (and apparently of rubber) where oxygenated gels and insoluble materials of high molecular weight are ultimately produced. Hence the elucidation of the mechanism of reaction in the simple examples is of considerable interest. This kind of polymerisation has been suspected to be a function of peroxidation or of peroxide breakdown (or both), but has not been clearly differentiated from the purely olefinic additions (involving carbon-to-carbon intermolecular linking) which constitute the ordinary thermal polymerisation reactions of unconjugated olefins, although much evidence shows that the thermal polymerisations require for their promotion temperatures well above 200°, whereas the autoxidation polymerisations can take place at ordinary or only moderately elevated temperatures.

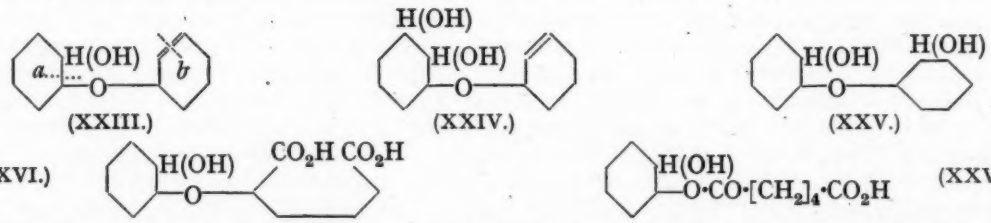
A preliminary examination of many " dimeric " residues from the hydroperoxides of *cyclo*hexene and methyl*cyclo*hexene has shown that these materials are highly heterogeneous, even although their average composition and molecular weight correspond closely with those required by the strict dimeric formula. This is seen if the residues are extracted with water and with dilute alkali, when usually three types of material, *viz.*, (i) neutral water-insoluble, (ii) neutral water-soluble, and (iii) acidic water-soluble, are obtainable. None of these fractions is entirely homogeneous, as distillation (with or without preliminary reduction of peroxide groups) shows, and hence the dimeride of even so simple a hydroperoxide as that of *cyclo*hexene must be recognised to contain a considerable range of individuals, formed either by interaction of different products in the autoxidation mixture or else by oxidative modification (with perhaps some dehydration) of the first-formed dimeric products.

The peroxide content of the residues has been found to depend considerably on the treatment, and especially the thermal treatment, they have received during their formation and isolation. It falls considerably (even as low as *ca.* 3%) when the original oxidation process or the subsequent distillation procedure is unduly prolonged or carried out at an unusually high temperature. Indeed, it is clear that heating at 70—100° causes fairly rapid progressive decomposition of the peroxide groups present (including those of unremoved monomeric hydroperoxide) with concomitant oxidative attack at the double bonds and rapid increase in the complexity of the system. Isolation of individual dimeric products by fractional distillation is thus well-nigh impossible, and even if all peroxide groups in an original oxidation product are reduced before any distillation is begun, the polymeric residue ultimately obtained is still heterogeneous.

A large proportion of the neutral, water-insoluble fraction obtained from the polymeric residues has a composition, when freed from residual peroxide groups by reduction, between $C_{12}H_{20}O_2$ and $C_{12}H_{18}O$ (as though a mixture of $C_{12}H_{20}O_2$ and its dehydration product), and is almost wholly non-saponifiable. The main bulk of the neutral, water-soluble material approximates in composition to $C_{12}H_{20}O_3$, and is hydroxylic and hygroscopic. The water-soluble acid fraction is hygroscopic and composed mainly of dimeric molecules of approximate average composition between $C_{12}H_{20}O_5$ and $C_{12}H_{20}O_6$ in which one of the six-carbon rings has apparently undergone oxidative scission, although small quantities of monomeric acidic material (chiefly adipic acid) have been isolated by distillation.

The basis of coupling of molecules appears to us probably to reside largely in the interaction of oxido-groups * in one reactant molecule (F) with hydroxylic groups in the other (G), and amongst the possible reactants derived from *cyclo*hexene in the two categories (F) and (G) are :

which may give rise to " dimeric " structures such as (XXIII)—(XXV) :



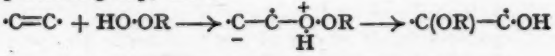
any of which may undergo some degree of dehydration, oxidative scission (*e.g.*, at *a* or *b* in XXIII), or oxidative hydroxylation (*e.g.*, at *b* in XXIII). Whether peroxido-links formed by interaction of oxido-groups and hydroperoxido-groups (RO>R'·O·O·H ⟶ OH·R·O·O·R') are produced at all is uncertain, but hydrogenation experiments indicate clearly that no considerable part of the dimeric product consists of dicyclyl peroxides (reducible to cyclic alcohols). So far as present experiments show, the bulk of the acidic dimeride is unsaponifiable, and is therefore to be regarded as composed of further-oxidised dimeride molecules such as (XXVI), rather than of dimeride molecules formed by interaction of an oxido-compound and a dibasic acid (*e.g.*, XXVII). The absence of any very large proportion of saponifiable material is probably to be expected in the autoxidation of a neutral olefin, since the production of free carboxylic acid by oxidative chain scission comes at a late stage in the autoxidation process, but such absence may well not hold in the case of the autoxidation of an unsaturated acid, where from the outset of reaction a large concentration of carboxyl groups is available. Indeed, Deatherage and Mattill (*Ind. Eng. Chem.*, 1939, **31**, 1425) have already observed that some considerable part of the autoxidation product of oleic acid is a saponifiable ester, yielding as the alcoholic component 9 : 10-dihydroxystearic acid, thus indicating that interaction between oxidostearic acid and the carboxyl group of oleic or oxygenated oleic acid has occurred. The constitution of oleic acid peroxide is described in Part IV.

There is, however, another likely mechanism of autoxidation polymerisation, which may play a more or less important part in the secondary changes (thermally or photochemically promoted) which destroy the first-formed hydroperoxide groups. In view of the ready thermal dissociation of dibenzoyl peroxide in liquid media to give free radicals, for which evidence is now strong, it seems probable that free-radical formation (R·OOH ⟶ RO— + —OH) enters into the normal decomposition of hydroperoxides, giving analogous results to those encountered with other decomposing systems (cf. Hey and Waters, *Chem. Rev.*, 1937, **21**, 169), and especially giving alcohols and ether-like dimerides (RO— + RH ⟶ ROH + R— and R·O·R + H—). The course of attack on *cyclo*hexene of the free radicals derived from dibenzoyl peroxide will be described later.

Experimental.

cyclo*Hexene Hydroperoxide.*—Carefully purified *cyclo*hexene, b. p. 83°, contained in a quartz flask connected with an oxygen reservoir, was warmed initially to 35°, shaken continuously, and irradiated by means of a

* It may not always be necessary for a hydroperoxide molecule first to decompose to the corresponding oxido-compound before it unites with another molecule. A direct route can be simply formulated whereby one of the reacting molecules requires as functional group a double bond (*e.g.*, an olefin, an olefin hydroperoxide, or an unsaturated alcohol) and the other a hydroperoxide group, thus :



An ether type of dimeride of somewhat variable constitution would still be formed.

Since any hydroperoxide molecule formed in the reaction mixture is normally surrounded by many olefin molecules and fewer hydroperoxide molecules (or their decomposition products), many " dimeric " molecules of type (XXIII) might well be produced.

mercury vapour lamp. For this purpose the flask, containing 100-g. or 200-g. portions of hydrocarbon, was mounted in a mechanical shaker above a small heating bulb, and placed about 6 inches from the lamp. The temperature in the flask usually remained between 35° and 40° without further external heating. The oxygen used was from a cylinder, and was roughly dried by passing through a calcium chloride tube placed between the reservoir and the reaction flask. No special precautions were taken to absorb small quantities of carbon dioxide produced in the oxidation. Usually, absorption of gas began immediately after the shaking and illumination were started, and proceeded at about 1,500 c.c. per hour. The purest peroxide was obtained by rapid absorption of oxygen over a comparatively brief period (3—4 hours), since prolonged exposure to ultra-violet light with the object of converting a larger portion of the hydrocarbon into peroxide produced large yields of a high-boiling alteration product, the so-called " dimer " of Stephens. Too slow absorption of oxygen over a long period, arising from feeble illumination (*e.g.*, diffused daylight or light from an ordinary electric bulb) or from a too low reaction temperature, invariably gave very impure peroxide (containing both low-boiling and high-boiling impurities) owing to the occurrence of secondary peroxidic transformation. In the earlier experiments the low-boiling impurities escaped notice owing to their high volatility and consequent inclusion with the recovered *cyclo*hexene. For the purpose of studying the secondary products a few oxidations were conducted more slowly, usually with feebler illumination.

The reaction mixture *always* contained (*a*) crude unchanged *cyclo*hexene, (*b*) a fraction of b. p. *ca.* 30°/0·2 mm., (*c*) the peroxide, and (*d*) some high-boiling material. These portions were isolated by a preliminary fractionation at 0·5 mm. pressure and then were examined separately. The peroxide fraction could be stored without any serious deterioration in a refrigerator; specimens of high peroxide content were often found to be little changed after storage for many weeks.

Fraction (b), *b. p.* 30°/0·2 *mm.*—Redistillation through a Dufton column gave a slightly syrupy, oxygenated liquid, b. p. 29—30°/0·2 mm., having P.O.C.* 3% (Found : C, 72·35; H, 10·3; iod. val., 198·0. Calc. for $C_6H_{10}O$: C, 73·4; H, 10·3%; iod. val., 259·2) and consisting largely of *cyclo*hexen-3-ol (α-naphthylurethane, m. p. 156°. Found : C, 76·1; H, 6·25; N, 5·35. Calc. for $C_{17}H_{17}O_2N$: C, 76·35; H, 6·4; N, 5·25%) together with a little *cyclo*hexene peroxide. The impure *cyclo*hexanol, after being shaken for a few minutes with 30% aqueous sodium sulphite to reduce *cyclo*hexene peroxide to *cyclo*hexenol, was then peroxide-free, but although it had the empirical formula $C_6H_{10}O$ (Found : C, 73·2; H, 10·2%) it still had only 78·3% of the required unsaturation and less than 80% of the required active hydrogen content (Found : iod. val., 207·5; active H, 0·82. Calc. for C_6H_9·OH : iod. val., 259·2; active H, 1·03%). The volatile, saturated, oxygenated impurity was the isomeride of *cyclo*hexenol, epoxy*cyclo*hexane.

The combined (*b*) fractions (10·1 g.) from two further portions of *cyclo*hexene which had been oxidised slowly under feebler illumination than usual were refractionated, a Dufton column being used. The major part boiled at 29—30°/0·2 mm. and again consisted of a similar mixture of *cyclo*hexenol, epoxy*cyclo*hexane, and a little peroxide (P.O.C. 2·9%; iod. val., 214·2). The epoxy*cyclo*hexane, owing to its high reactivity when heated, and especially its ready oxidisability, could best be isolated when the crude oxidation product was immediately reduced with sodium sulphite before fractionation was carried out (see below).

When 2 g. of fraction (*b*) which had been freed from peroxide by sodium sulphite were heated with 15 c.c. of water for 4 hours at 115° in a sealed tube in order to hydrolyse the epoxide, *cyclo*hexen-3-ol and a crude water-insoluble " dimeric " *oil*, b. p. 112°/0·2 mm. (Found : C, 75·6; H, 10·0; iod. val., 180·0. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·3%) were obtained. When a further 2-g. portion of peroxide-free fraction (*b*) was hydrolysed by warming with 20 c.c. of N-sulphuric acid for 48 hours at 40—45°, *cyclo*hexenol together with a similar " dimeric " oil (Found : C, 78·35; H, 10·2%; iod. val., 213·5) were obtained. Several repetitions of these hydrolyses using (*b*) fractions isolated from other oxidation products always failed to give more than very small yields of *cyclo*hexane-1 : 2-diol, showing that the epoxide was destroyed by either procedure, and apparently underwent reaction with *cyclo*hexanol to give the " dimeric " oil. The formation of epoxy*cyclo*hexane was more easily demonstrated by examination of fraction (*a*).

Fraction (c).—Rapid oxidation of *cyclo*hexene during 4 hours usually gave a product from which were obtained on first fractionation a peroxide fraction of P.O.C. 20—25%, and on second fractionation a 15—20% yield (based on the hydrocarbon taken) of substantially pure *cyclo*hexene 3-hydroperoxide, b. p. 47—48°/0·2 mm. (Found : C, 63·25; H, 8·85; P.O.C., 28·0. Calc. for $C_6H_{10}O_2$: C, 63·1; H, 8·85%; P.O.C., 28·05%), together with a little less pure (mostly rather low-boiling) peroxide. The unsaturation of the peroxide was conveniently determined by iodine value, but was always a little low (*ca.* $\overline{|}_{0\cdot94}$), owing in part to the occurrence of subsidiary reaction between the peroxide and the potassium iodide reagent. On hydrogenation (Adams's catalyst) the peroxide absorbed 2 mols. of hydrogen, giving, in nearly quantitative yield, immediately crystallisable *cyclo*hexanol [3 : 5-dinitrobenzoate, m. p. 110°, mixed m. p. 110° (Found : C, 53·3; H, 4·75; N, 9·60. Calc. for $C_{13}H_{14}O_6N_2$: C, 53·05; H, 4·8; N, 9·5%); α-naphthylamine complex with the dinitrobenzoate, m. p. 126°, mixed m. p. 126° (Found : C, 62·8; H, 5·1; N, 10·05. Calc. for $C_{23}H_{23}O_6N_3$: C, 63·15; H, 5·3; N, 9·6%)]. The

* The peroxidic oxygen content is referred to as P.O.C. and denotes the percentage of oxygen per mol. which is contained in ·(OOH) groups, *i.e.*, twice the percentage of active oxygen per mol. A rapid and convenient method of P.O.C. determination has been devised for use in these investigations by Bolland, Sundralingam, Sutton, and Tristram (*Trans. Inst. Rubber Ind.*, 1941, **16**, 29).

rather low-boiling fractions of peroxide showed a low P.O.C. and absorbed only about 1 mol. (usually 0·95—0·98 mol.) of hydrogen; the hydrogenation product gave, after removal of a small volatile forerun, homogeneous *cyclo*hexanol. This confirmed that the principal normal decomposition product of *cyclo*hexene peroxide is *cyclo*hexenol; and since in slow oxidations the yield of pure peroxide was diminished and that of the low-boiling fractions increased, the conditions for slow oxidation promoted considerable decomposition.

For the efficient reduction of considerable quantities of the peroxide to *cyclo*hexenol, the former was shaken with well-cooled 30% aqueous sodium sulphite solution, at first cautiously to avoid undue heat development, and later for 2—3 hours on a mechanical shaker. The alcohol, when extracted with ether and rectified, boiled at 65—66°/13 mm.

Fraction (a), *b. p.* 60°/100 *mm.*—To avoid the formation of additional by-products or the destruction of the original ones through being heated with peroxide during fractional distillation, the reaction product from 100 g. of hydrocarbon (5 hours oxidation; weight increase, 9·0 g.) was reduced immediately with 30% aqueous sodium sulphite, the reduced product extracted with ether, dried, and freed first from solvent, and then (at slightly reduced pressure) from *cyclo*hexene. The peroxide-free oxidation product gave on fractionation at reduced pressures under a short column the fractions: (i) b. p. below 60°/13 mm. (5·0 g.), (ii) b. p. 64—65°/12 mm. (13·1 g.), (iii) b. p. 80—86°/1 mm. (2·1 g.), (iv) b. p. 94—95°/1 mm. (0·3 g.), and a residue (*ca.* 1 g.). Of these (ii) was almost pure *cyclo*hexenol of nearly correct unsaturation and analytical composition (α-naphthylurethane, m. p. 156°; mixed m. p. 156°), (i) was a mixture of this with much epoxy*cyclo*hexane, and the higher fractions consisted of heterogeneous " dimeric " materials. The epoxide fraction gave a good yield of *trans-cyclo*hexane-1 : 2-diol, m. p. 104°, mixed m. p. 104°, on hydrolysis at 40—45° with N-sulphuric acid, and the largest " dimeric " fraction had (assuming homogeneity) an empirical composition approximating to $C_6H_{10}O$ (Found: 77·7; H, 10·2; iod. val., 130·8. Calc. for $C_6H_{10}O$: C, 73·4; H, 10·3%). Repetition of the experiment with 100 g. of *cyclo*hexene gave precisely comparable results, the yield of epoxide being substantial and the fraction (iii) now giving: C, 75·2; H, 10·1%; iod. val., 140.

An attempt to fractionate a further 10 g. of the epoxide fraction at atmospheric pressure caused considerable interaction of the component materials as well as dehydration, with formation of (i) a small quantity of highly unsaturated hydrocarbon, apparently *cyclo*hexadiene, (ii) *cyclo*hexane-1 : 2-diol, m. p. 104° (Found: C, 62·0; H, 10·4. Calc. for $C_6H_{12}O_2$: C, 62·0; H, 10·4%), and a viscous residual liquid. A tolerably pure epoxide fraction, of b. p. 110—120°, convertible into *cyclo*hexanediol, was, however, obtained.

Action of Heat on the Hydroperoxide.—When *cyclo*hexene hydroperoxide was heated, its peroxidic character diminished. The change was relatively slow at room temperature in diffused daylight, but much more rapid when the peroxide was distilled from a bath at 70—80°. A peroxide fraction (16·5 g.) which, when separated from the crude oxidation product by one distillation at 0·5 mm. pressure, had P.O.C. 24·2%, gave on redistillation at the same pressure the fractions (i) b. p. 30—35°, P.O.C. 2—3% (1·8 g.); (ii) b. p. 44—45°, P.O.C. 20·1% (10 g.); (iii) b. p. 45—46°, P.O.C. 28·5% (3·6 g.); and a high-boiling residue (0·8 g.). The chief low-boiling product was *cyclo*hexen-3-ol, but no epoxy*cyclo*hexane was identified. The high-boiling residue approximated in composition to the formula $C_6H_{10}O_2$ (Found: C, 63·75; H, 9·05. Calc. for $C_6H_{10}O_2$: C, 63·1; H, 8·85%) and had P.O.C. 14·3%: it thus corresponded with Stephens's " dimeride."

Action of Ultra-violet Light on the Hydroperoxide.—Peroxide of P.O.C. 27·8% (4. g.) was placed in a quartz flask and the air carefully displaced by oxygen-free nitrogen. The flask was shaken and simultaneously illuminated by ultra-violet light at about 35° for 6 hours. The viscosity of the peroxide increased, its colour changed to light yellow, and its P.O.C. fell by about half to 14·5%; its empirical composition, however, was little or not at all changed (Found: C, 63·8; H, 9·0%). A portion (2·8 g.) of the irradiated material was immediately hydrogenated in alcohol (Adams's catalyst). It absorbed 559 c.c. at N.T.P., *i.e.*, half of that required (1090·4 c.c.) for reducing one double bond and the ·OOH group in C_6H_9·OOH. In view of the observed overall fall of one half of the total P.O.C., due to irradiation, the overall olefinic unsaturation must likewise have diminished by one-half (282 c.c. of hydrogen at N.T.P. used for reducing peroxide, 277 c.c. for reducing double bond). Thus an overall loss by decomposition of one hydroperoxide group was accompanied by the saturation of one double bond. The product, when freed from alcohol, had P.O.C. < 0·02%; it gave on distillation (i) 1·1 g. of *cyclo*hexanol, b. p. 63—64°/14 mm. (ii) 0·6 g. of " dimeric " material, b. p. 110—176°/0·5 mm., and (iii) 0·4 g. of undistilled residue.

3·2 G. of peroxide of P.O.C. 27·8% (Found: C, 63·2; H, 9·0%) were irradiated for 6 hours at *ca.* 35° as above, but in an atmosphere of oxygen. Some oxygen was absorbed (150 c.c.) and the pale yellow liquid product then had P.O.C. 14·35% [Found: C, 58·75; H, 8·2; O (by diff.), 33·05%]. On hydrogenation the product (2·6 g.) absorbed 403 c.c. (average of 0·64 mol.) of hydrogen at N.T.P., so during the irradiation both absorption of oxygen and some saturation of the double bond had occurred. The product consisted of a little *cyclo*hexenol (0·6 g.) and " dimeric " material of b. p. 120°/0·5 mm. and above.

Action of the Hydroperoxide on cyclo*Hexene.*—When equimolecular amounts of the peroxide (3·9 g.) and pure hydrocarbon (2·8 g.) were exposed in a flask to diffused daylight for 4 weeks at room temperature, and the product subsequently hydrogenated, it was found to have undergone no serious reduction of unsaturation (H_2 absorbed, 2250 c.c. at N.T.P.; theory, 2295 c.c.). When a similar mixture (3 g. of each component) was heated for 5 hours on a water-bath, the product was found on fractionation to consist of crude *cyclo*hexene

(2·4 g.), *cyclo*hexenol (0·8 g.), unchanged peroxide (1·4 g.), "dimer" (0·4 g.), and undistilled residue (0·5 g.). After the lowest-boiling fractions had been heated with water at 115° in a sealed tube to hydrolyse any epoxy-*cyclo*hexane present, only a small yield of *cyclo*hexane-1 : 2-diol, m. p. 104°, could be isolated from the product.

Action of the Hydroperoxide on cyclo*Hexen-3-ol.*—The alcohol (3·4 g.) and pure peroxide (3·5 g.) were heated together at 100° for 5 hours. The pale yellow liquid product was reduced with sodium sulphite solution and fractionated. The product consisted almost entirely of *cyclo*hexenol, but there were a small fraction (0·3 g.) of b. p. 100—105°/13 mm. and a higher-boiling residue (0·3 g.). The volatile fraction gave on heating with water in a sealed tube at 110° a small yield of *cyclo*hexane-1 : 2 : 3-triol (see below). No oxidation of *cyclo*hexenol to *cyclo*hexenone had occurred.

A similar mixture of alcohol and hydrocarbon in a quartz flask was shaken and simultaneously exposed to ultra-violet light at 35° in a nitrogen atmosphere. The product, after being freed from peroxide by shaking it with sodium sulphite, was fractionated: it consisted of *cyclo*hexenol (76%) and "dimeric" material, of b. p. 110°/13 mm. and above. No ketone was detected.

Action of Dilute Sulphuric Acid on the Hydroperoxide.—Crude, undistilled *cyclo*hexene hydroperoxide, derived by slow oxidation of *cyclo*hexene under feeble ultra-violet illumination (24 hours at 30—40°) and freed from unchanged *cyclo*hexene by distillation at 12 mm. pressure (4 g.), was mixed with N-sulphuric acid (20 c.c.) and kept at 40—45° for 1 week. The undissolved oil was collected with a little ether, and the clear aqueous layer then neutralised and evaporated to dryness. The residue yielded (*a*) by extraction with ethyl acetate crude *cyclo*hexanetriol, b. p. 115—120°/1 mm. (1 g.), which on crystallisation from ethyl acetate melted at 108—111° and on recrystallisation at 124° (Found: C, 54·65; H, 9·2. Calc. for $C_6H_{12}O_3$: C, 54·5; H, 9·15%), and (*b*) by acidification, followed by extraction with ether, a syrupy acidic oxidation product of high b. p. The water-insoluble oil when worked up gave *cyclo*pentene-1-aldehyde, b. p. 55—60°/13 mm. (0·6 g.) [dimedone, m. p. 123—124°; semicarbazone, m. p. 209° (Found: C, 54·5; H, 7·25; N, 26·7. Calc. for $C_7H_{11}ON_3$: C, 54·85; H, 7·25; N, 27·45%)], *cyclo*hexenol contaminated with a little unchanged peroxide, b. p. 65—70° (0·5 g.), and higher-boiling hydroxylic "dimeric" materials (1·6 g.). Repetitions of the experiment with hydroperoxide of correct or slightly low P.O.C. gave also *cyclo*hexanetriol (35—45% yield), *cyclo*hexenol (10—15%), water-insoluble hydroxylic oils, for the most part distillable (b. p. 70—100°/13 mm.) (*ca.* 10—15%), syrupy acidic material (*ca.* 10% yield), and always some *cyclo*pentenealdehyde. The yield of aldehyde increased considerably with decreasing P.O.C. of the hydroperoxide specimen but was never less than 2—3% even when derived from specimens of correct P.O.C.

Action of Water on the Hydroperoxide.—When the hydroperoxide (5·3 g.) of P.O.C. 17% was heated for 3 hours with water in a sealed tube at 115°, a brown oily layer (3·2 g.) and an aqueous layer resulted. The former when distilled gave *cyclo*pentene-1-aldehyde (0·8 g.) and about equal quantities of unchanged hydroperoxide, *cyclo*hexenol, and "dimeric" oil; the latter, on extraction with ethyl acetate, gave *cyclo*hexanetriol (1 g.) and a distillable hygroscopic syrupy acid (0·5 g.). The last of these was a non-homogeneos oxidation product, b. p. *ca.* 100°/2 mm. (Found: C, 58·65; H, 8·55%).

Action of Caustic Alkali on the Hydroperoxide.—The peroxide (9·3 g.) of P.O.C. 27·0%, when mechanically shaken with N-sodium hydroxide (150 c.c.) for 2 hours, dissolved to give a yellow solution. The product after having stood for 24 hours at room temprature gave on extraction with ether *cyclo*hexen-3-ol (6·6 g.; 82% yield). The alkaline liquor on acidification and extraction with ether gave a very small yield of adipic acid, m. p. 152° (mixed m. p. 152°), and some syrupy acid; a further amount of syrupy acid was obtained by continuous extraction with ether. The nature of this heterogeneous syrupy acid has been investigated by Hock and Gänicke (*loc. cit.*).

1-*Methyl*cyclo*hexene Hydroperoxide and its Transformation Products.*

1-*Methyl*cyclo*hexene Hydroperoxide*, 1-*Methyl*cyclo*hexene* 1 : 2-*Epoxide and* 1-*Methyl*cyclo*hexenol.*—Methyl*cyclo*hexene, b. p. 110—111° (90 g.), obtained by dehydration of 1-methyl*cyclo*hexanol in presence of a little iodine, was oxidised in a quartz flask at *ca.* 35°, as described for *cyclo*hexene (above). Absorption of gas occurred rapidly (1·5—2·5 l. per hour; 9,800 c.c. in 5½ hours), and the product gave on distillation at 15 mm. pressure unchanged methyl*cyclo*hexene (50 g.; nearly 60% recovery) and colourless, crude peroxide (39·1 g.). The latter gave on fractionation at 0·2 mm.: (i) b. p. 40—41°, P.O.C. 4·9% (11·8 g.), (ii) b. p. 52—58°, P.O.C. 20·95% (6·6 g.), (iii) b. p. 60—67°, P.O.C. 26% (5·0 g.), (iv) b. p. 67—70°, P.O.C. 24·0% (15·7 g.), and a "dimeric" residue, P.O.C. *ca.* 25% (15·0 g.).

The fraction (i), when freed from peroxide with sodium sulphite solution, was a volatile non-ketonic liquid (unreactive with the Girard reagent "T"), b. p. 65—67°/13 mm., having nearly the empirical composition of methyl*cyclo*hexenol but less than half its unsaturation (Found: C, 74·05; H, 10·95; iod. val., 103·9, 104·3. Calc. for $C_7H_{12}O$: C, 74·95; H, 10·7; iod. val., 226·9). This was a mixture of methyl*cyclo*hexenol (about 50%) with 1-methyl*cyclo*hexene 1 : 2-epoxide, and gave on hydrolysis with N-sulphuric acid (2·2 g. warmed with 15 c.c. of acid for 1 week at 40—45°) a 30% yield of *trans*-1-methyl*cyclo*hexane-1 : 2-diol (prisms, m. p. 84°, from light petroleum–chloroform; lit., m. p. 83·5°) (Found: C, 64·6; H, 11·0. Calc. for $C_7H_{14}O$: C, 64·6; H, 10·85%), together with a little methyl*cyclo*hexenol, b. p. 66—67°/13 mm. (0·3 g.) (see below) and a "dimeric" fraction, b. p. 130—132°/13 mm. (0·5 g.). Hydrolysis of a similar epoxide–alcohol fraction with water at 115° gave a similar result, but a smaller yield of diol.

The fraction (iii) consisted of nearly pure 1-*methyl*cyclo*hexene* 6 (with some 3)-*hydroperoxide* (P.O.C., 26. $C_7H_{12}O_2$ requires P.O.C., 25%), and fraction (iv) was only a little inferior in P.O.C. to (iii). Redistillation caused some secondary change, involving decomposition of the peroxide groups in a part of the material. The fraction of b. p. 64—67°/0·2 mm. so obtained had P.O.C. 99% of theory but was not quite pure (Found: C, 66·1; H, 9·75; active H, 0·85. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4; active H, 0·78%).

When the hydroperoxide (3·6 g.) was shaken with 30% aqueous sodium sulphite (200 c.c.) for 3 hours and then similarly treated with fresh sulphite, reduction (less facile than with *cyclo*hexene hydroperoxide) occurred. The product, when extracted with ether, and dried, gave on distillation 1-*methyl*cyclo*hexen*-6(with some 3)-*ol* containing a little of a saturated secondary product (Found: C, 74·0; H, 10·1; iod. val., 206·3, 208·0. $C_7H_{12}O$ requires C, 74·95; H, 10·7%; iod. val., 226·7). The impure alcohol gave an oily 3:5-dinitrobenzoate from which a crystalline α-naphthylamine *complex*, m. p. 95—96° (Found: N, 9·35. $C_{24}H_{23}O_6N_3$ requires N, 9·35%), was obtained.

Hydrogenation of the hydroperoxide (11·6 g.; P.O.C. 22%) in alcohol by means of Adams's catalyst took place more slowly than with *cyclo*hexene hydroperoxide. After 18 hours, 3720 c.c. of hydrogen at N.T.P. had been absorbed (Calc. for $\equiv_{0·88}$ and 0·88 ·OOH group in peroxide of P.O.C. 22%: 3572 c.c.). The centrifuged product gave on distillation crude 1-methyl*cyclo*hexanol, b. p. 60—76°/13 mm. (Found: C, 71·85; H, 11·65. Calc. for $C_7H_{14}O$: C, 73·35; H, 12·3%), the *α-naphthylurethane* from which contained two difficultly-separable isomerides. Two crystallisations of the urethane from petroleum (b. p. 60—80°) gave a product, m. p. 123° (Found: C, 76·6; H, 7·65; N, 5·3. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·4; N, 5·0%), which depressed the m. p. of the urethane of authentic 1-methyl*cyclo*hexane-3-ol (m. p. 123°; mixed m. p. 102°) but apparently consisted mainly of the urethane of 1-methyl*cyclo*hexan-2-ol (m. p. 154°; mixed m. p. 139°). Oxidation of the crude alcohol in aqueous acetic acid with chromic acid gave a ketone, b. p. 80—86°/60 mm., the semicarbazone from which melted at 175°, and after two crystallisations from methyl alcohol at 191° (Found: C, 56·6; H, 9·1. Calc. for $C_8H_{15}ON_3$: C, 56·8; H, 8·94%). This was identical with the semicarbazone of authentic 1-methyl-*cyclo*hexan-2-one, m. p. 192° (mixed m. p. 191—192°). The mother-liquors of both urethane and semicarbazone each contained a second derivative in minor amount, difficultly purifiable, but in view of later observations (below), without doubt derived from 1-methyl*cyclo*hexan-3-ol and -3-one, respectively. It follows, therefore, that the hydroperoxide and methyl*cyclo*hexenol derived from 1-methyl*cyclo*hexene contained both the 6-substituted (major) and the 3-substituted (minor) isomerides.

Action of Dilute Sulphuric Acid on the Hydroperoxide.—The hydroperoxide (4 g.) was warmed to 45° for 100—120 hours with N-sulphuric acid (20 c.c.). The product contained an oily and an aqueous layer. The latter gave on neutralisation with alkali, evaporation, and extraction with ether, 1-*methyl*cyclo*hexane*-1:2:3-*triol*, b. p. 152—154°/1 mm., crystallising from ethyl acetate in small prisms, m. p. 95° (1·9 g.) (Found: C, 57·1; H, 9·55. $C_7H_{14}O_3$ requires C, 57·5; H, 9·6%), and the former on distillation at 13 mm. pressure gave three fractions, of b. p. 58°, 80—90°, and 114—120°, severally. The first of these fractions was a slightly impure ketone, $C_7H_{10}O$ (Found: C, 75·35; H, 9·3. Calc.: C, 76·3; H, 9·15%), recognised by its semicarbazone, m. p. 205° (Found: C, 57·3; H, 7·75; N, 24·9. Calc. for $C_8H_{13}ON_3$: C, 57·45; H, 7·8; N, 25·15%), and oxime, m. p. 91° (Found: C, 67·1; H, 8·7; N, 11·3. Calc. for $C_7H_{11}ON$: C, 67·15; H, 8·85; N, 11·2%), to be 1-acetyl*cyclo*pentene (Wallach, *Annalen*, 1909, **365**, 275, reports semicarbazone, m. p. 203—204°, and oxime, m. p. 91°). The higher-boiling fractions consisted of a little crude methyl*cyclo*hexenol containing unchanged peroxide and " dimeric " products. The neutral sodium salts gave on acidification and extraction with ether a syrupy, acidic product.

Action of Caustic Alkali on the Hydroperoxide.—When the hydroperoxide (6·4 g.) was shaken for 3 hours with N-sodium hydroxide (150 c.c.), kept overnight, and then warmed at 30° for 3 hours, an oil which proved to be a mixture of 6- and 3-hydroxy-1-methyl*cyclo*hexene separated and was collected in a little ether. The crude alcohol was re-treated with alkali to remove the last traces of peroxide, and then distilled. It boiled at 66—68°/13 mm. (Found: C, 74·5; H, 10·55. Calc. for $C_7H_{12}O$: C, 74·95; H, 10·7%); yield 89%. The alkaline solution gave on neutralisation, evaporation, and final extraction with ether of the acidified residue, a brown syrupy acid (1·0 g.), from which some large prisms of a monobasic *acid*, $C_7H_{10}O_2$, m. p. 207°, separated (Found: C. 66·6; H, 8·0; equiv., 125·7. $C_7H_{10}O_2$ requires C, 66·65; H, 8·0%; equiv., 126·0). The solid acid remained unattacked when shaken in alcohol with hydrogen and Adams's catalyst; it was, however, readily attacked by permanganate, giving thereby an acid of high oxygen content ($?C_7H_{12}O_6$), crystallising in minute stout plates, m. p. 69°, but obtained in too small amount to be adequately examined. The residual syrupy acid was heterogeneous, a minor part consisting of γ-acetylbutyric acid, isolated in the form of its hydrated semicarbazone, $C_7H_{13}O_3N_3,H_2O$, of m. p. 170° (decomp.) (slow heating), which became anhydrous at 100° (cf. Dieckmann, *Ber.*, 1912, **45**, 2704; Dupont, *Bull. Soc. chim. Belg.*, 1936, **45**, 57; *et al.*) (Found: C, 45·15; H, 6·9. Calc. for $C_7H_{13}O_3N_3$: C, 44·9; H, 7·0%), and the major part persisting as an intractably syrupy acid which was not further examined.

1:2-*Dimethyl*cyclo*hexene* 3-*Hydroperoxide and its Transformation Products.*

1:2-*Dimethyl*cyclo*hexene* 3-*Hydroperoxide*, 1:2-*Dimethyl*cyclo*hexene* 1:2-*Epoxide*, *and* 1:2-*Dimethyl*-cyclo*hexen*-3-*ol*.—Dimethyl*cyclo*hexene, b. p. 136—137° (71 g.), obtained by dehydration in presence of iodine

of 1 : 2-dimethyl*cyclo*hexan-1-ol, formed from 2-methyl*cyclo*hexanone and methylmagnesium iodide, was oxidised at 23° in a quartz flask. In 95 mins., 5·81. (7·5 g.) of oxygen were absorbed. Distillation of unchanged hydrocarbon (41·5 g.) gave a residue of crude oxygenated products (35·6 g.) which on fractionation at 0·5 mm. pressure gave the fractions: (i) b. p. 40—50° (5·1 g.; P.O.C., 4·8%), (ii) b. p. 55—64° (8·8 g.; P.O.C., 19·4%); (iii) b. p. 64—69° (6·4 g.; P.O.C., 23·5%); (iv) b. p. 70—73° (6·1 g.; P.O.C., 22·3%), and a heterogeneous " dimeric " residue (6·0 g.; P.O.C., 9·8%). Of these fractions, (iii) and (iv) consisted of practically pure 1 : 2-*dimethyl*cyclo*hexane* **3-*hydroperoxide***, b. p. 67—70°/0·5 mm. (Found: C, 67·7; H, 9·9. $C_8H_{14}O_2$ requires C, 67·55; H, 9·9; P.O.C., 22·2%), and fraction (ii) also consisted mainly of hydroperoxide. Fraction (i), when it had been entirely freed from traces of unchanged hydroperoxide by treatment with sodium sulphite, and refractionated, gave a low-boiling portion containing 30—40% of a saturated component, and a higher-boiling portion (2·5 g.) of nearly pure dimethyl*cyclo*hexen-3-ol (iod. val., 191·5. Theory, 201·5), oxidisable to dimethyl*cyclo*hexen-3-one (see below). The lower-boiling portion was crude 1 : 2-dimethyl*cyclo*hexene 1 : 2-epoxide and gave on hydrolysis with N-sulphuric acid *trans*-1 : 2-dimethyl*cyclo*hexane-1 : 2-diol, m. p. 92° (0·5 g.) (Found: C, 66·4; H, 11·25. Calc. for $C_8H_{16}O_2$: C, 66·6; H, 11·2%). Refractionation at atmospheric pressure of the unchanged hydrocarbon, after it had been well dried with anhydrous magnesium sulphate (calcium chloride proved unsatisfactory), gave 4 g. of crude epoxide from which by hydrolysis with sulphuric acid the *trans*-diol, m. p. 92° (1·5 g.) was obtained.

Action of Dilute Sulphuric Acid on the Hydroperoxide.—The hydroperoxide (4·6 g.), when treated with N-sulphuric acid as above, gave a water-soluble fraction (2·0 g.) and a water-insoluble fraction (2·6 g.). The former gave on distillation at 0·5 mm. pressure 1 : 2-*dimethyl*cyclo*hexane*-1 : 2 : 3-*triol*, which crystallised from ethyl acetate–ether in colourless prisms, m. p. 109° (Found: C, 59·8; H, 10·1. $C_8H_{16}O_3$ requires C, 60·0; H, 10·1%); the latter gave on distillation (i) a ketonic fraction (free from aldehyde) of b. p. 74—80°/13 mm. (0·93 g.), (ii) an alcohol, identified as somewhat impure 1 : 2-dimethyl*cyclo*hexen-3-ol (see above), and (iii) a small " dimeric " residue. The ketone yielded a semicarbazone and an oxime which, when recrystallised from alcohol, melted respectively at 219° and 85°. These compounds proved on direct comparison to be identical with the corresponding derivatives (m. p.'s 221° and 86° respectively) of 1-acetyl-2-methyl*cyclo*pentene, the requisite ketone (b. p. 72—74°/13 mm.) being synthesised from 1 : 2-dimethyl*cyclo*hexene by successively ozonising it, heating the ozonide with water, and finally heating the resulting 1 : 4-diacetylbutane (b. p. 110°/13 mm.) with either N-sulphuric acid or alcoholic potassium hydroxide.

Action of Caustic Alkali on the Hydroperoxide.—The hydroperoxide was shaken with N-sodium hydroxide solution for 3—4 hours, and the mixture first allowed to stand overnight and then warmed to 30—40° for 2 hours. The product when worked up gave an alcohol (80% yield) and a syrupy acid (15—20% yield). The alcohol, after being freed from a little unchanged peroxide by renewed shaking with alkali, proved to be 1 : 2-*dimethyl*cyclo*hexen*-3-*ol*, b. p. 80—82°/13 mm. (Found: C, 75·35; H, 11·5; iod. val., 202. $C_8H_{14}O$ requires C, 76·1; H, 11·2%; iod. val., 201·5). This gave an *α-naphthylurethane*, m. p. 139—140° (Found: C, 77·0; H, 7·3. $C_{19}H_{21}O_2N$ requires C, 77·25; H, 7·15%), was oxidisable by chromic acid to 1 : 2-dimethyl*cyclo*hexene-3-one [semicarbazone, m. p. 224—225° (Kötz *et al.*, *Annalen*, 1913, **400**, 83, give m. p. 225°). Found: C, 59·4; H, 8·4. Calc. for $C_9H_{15}ON_3$: C, 59·6; H, 8·35%], and absorbed 1 mol. of hydrogen per mol. in presence of palladium–charcoal. The syrupy acid deposited (on one occasion only) a few colourless prismatic crystals, insufficient for adequate purification, of an acid, m. p. 196—197° (Found: C, 65·45; H, 7·95%), which was similar to, or possibly identical with, the acid of m. p. 207° derived similarly from 1-methyl*cyclo*hexene hydroperoxide; the main bulk, however, always consisted of γ-acetylbutyric acid [semicarbazone, m. p. 170°, identical with that obtained above in a corresponding way from 1-methyl*cyclo*hexene hydroperoxide (Found: C, 44·65; H, 6·9%)].

Rapid Decomposition of Peroxides.

cyclo*Hexene Hydroperoxide.*—When a few mg. of ferrous phthalocyanine were dropped into portions of 4 g. of fairly pure peroxide there was usually a flash of light, and always the liquid became warm and soon boiled. A little water separated, the liquid darkened in colour, and aldehydic vapour but no oxygen was evolved. Direct distillation of the liquid products when reaction subsided caused renewed reaction, with formation of much high-boiling material: it was better to extract the main products with light petroleum, leaving behind the catalyst and a little ether-soluble oxidation product. Distillation at reduced pressure then gave, first, a fraction of strong aldehydic odour and reaction, and later, fractions which contained much *cyclo*hexenol and unchanged peroxide. The aldehydic fraction, b. p. 60—62°/14 mm., was heterogeneous, giving a crude semicarbazone, m. p. 155—165°, containing two isomerides $C_7H_{11}ON_3$ (Found: C, 54·95; H, 7·25. Calc.: C, 54·85; H, 7·25%). By repeated recrystallisation from alcohol, the higher-melting component, m. p. 205°, was isolated in small yield and identified as *cyclo*pentene-1-aldehydesemicarbazone; the major component, however, could not be fully freed from its isomeride (m. p. 157—163°) and appeared to consist mainly of *cyclo*hexen-3-onesemicarbazone, m. p. 161°.

When the hydroperoxide was gradually heated in an open test-tube, standing in an oil-bath, very vigorous decomposition set in at about 120°, steam and volatile vapours being evolved, the latter containing *cyclo*pentene-1-aldehyde.

1-*Methyl*cyclo*hexene Hydroperoxide.*—Treatment of this peroxide with ferrous phthalocyanine as above caused development of heat, darkening in colour, and vigorous ebullition. The products, if freed from catalyst before being distilled, were almost completely distillable. The b. p. of the distillate rose progressively from 80°/13 mm. to 122°/11 mm. No exhaustive examination of the fractions was made, but much of the material consisted of methyl*cyclo*hexenol and unchanged hydroperoxide; the fractions boiling between 64° and 78° at 1 mm., however, contained a moderate proportion of ketone, which gave mixtures of two semicarbazones, (1) m. p. 207—208° (slow heating), identified as 1-methyl*cyclo*hexen-6-one semicarbazone (m. p. 207—208°; Wallach, *Annalen*, 1908, **359**, 303. Found: C, 57·5; H, 7·95. Calc. for $C_8H_{13}ON_3$: C, 57·45; H, 7·85%) by comparison with the semicarbazone of the ketone formed by oxidation of 1-methyl*cyclo*hexen-6-ol with chromic acid (mixed m. p. 207—208°), and (2) m. p. 198—200°, rather more readily soluble in alcohol than (1). This last compound appeared to be isomeric with both (1) and 1-acetyl*cyclo*pentenesemicarbazone (m. p. 207—208°; mixed m. p. 190—192°), and hence was probably 1-methyl*cyclo*hexen-3-one semicarbazone (m. p. 198°, 199—200°; Fargher and Perkin, J., 1914, **105**, 1362) (Found: C, 57·35; H, 8·0%).

1 : 2-*Dimethyl*cyclo*pentene Hydroperoxide.*—This peroxide when similarly decomposed with ferrous phthalocyanine gave a comparable heterogeneous product, the most volatile portion of which, b. p. 56—63°/1 mm., contained a ketonic component. This formed a semicarbazone, m. p. 219°, raised by recrystallisation from alcohol to 224—225°. This semicarbazone closely resembled in physical properties authentic 1 : 2-dimethyl-*cyclo*hexen-3-one semicarbazone, m. p. 224—225°, derived by oxidation of 1 : 2-dimethyl*cyclo*hexen-3-ol with chromic acid; also it caused no depression of m. p. when heated with the latter. On the other hand, it depressed the m. p. of authentic 1-acetyl-2-methyl*cyclo*pentenesemicarbazone, m. p. 221° (mixed m. p. 209°).

Dimeric Products.

From cyclo*Hexene Hydroperoxide.*—From all autoxidation products there remained after distillation of the hydroperoxides at 0·2—1·0 mm. pressure a rather viscous, yellow, peroxidic oil which was partly distillable below 1 mm. pressure. The proportion of this polymeric residue varied considerably (from 25% to 40% of the total oxygenated material) with change in the conditions of oxidation, and increased markedly with prolongation of heating during the oxidation or distillation, and apparently also with prolongation of exposure to ultra-violet light. When the *crude* oxidation product was freed from active peroxide groups by reduction with sodium sulphite immediately the absorption of oxygen ended, the yield of dimeric material on subsequent distillation fell to 15—20%. Each time the pure hydroperoxide was distilled, a fresh small quantity of high-boiling residue was left; furthermore, when the carefully fractionated hydroperoxide was irradiated for several hours in an atmosphere of pure nitrogen, a considerable high-boiling, yellow residue remained on distillation.

When oxidation was conducted rapidly at *ca.* 30—35° and the monomeric products were removed as efficiently and rapidly as possible at pressures below 1 mm., the residue (*undistilled*) approximated in average composition to that required for the empirical formula $C_6H_{10}O_2$, as shown by analytical data from residues from three sources: (*a*) From normal oxidation (Found: 63·85; H, 8·95; P.O.C., 14·7%; iod. val., 122·0. Calc. for $C_{12}H_{20}O_4$: C, 63·2; H, 8·8; iod. val., for $\frac{1}{2}$, 222·8; P.O.C. for 2 ·OOH groups, 28·6%); (*b*) from irradiation of hydroperoxide in nitrogen (Found: C, 63·8; H, 9·0; P.O.C., 14·5%); (*c*) from redistillation of rectified hydroperoxide (Found: C, 63·75; H, 9·85; P.O.C., 12·65%). When the oxidation was conducted at higher temperatures (*e. g.*, 50—60°) or the process was unduly prolonged owing to use of feeble irradiation, or temperatures well above 70° were used in distilling off the monomeric hydroperoxide, then the P.O.C. of the residue was low, ranging down to 3%. Direct heating of the residue for a short time at 100° caused marked decrease in P.O.C. Since there was great difficulty in completely distilling the monomeric peroxide from the residue, whilst avoiding excessive heating, the figures for the P.O.C. of the polymeric material (distillation bath below 80°) were probably somewhat high.

Fractional distillation at 0·5 mm. pressure of a normal oxidation residue having P.O.C. 12·6% gave fractions of both varied boiling point (from 40° to 98°) and P.O.C., leaving a brown, almost peroxide-free mass in the still. Fractional distillation of a similar residue which had first been reduced to nearly zero P.O.C. with sodium sulphite gave on distillation fractions ranging in b. p. from 50° to 130° at 0·5 mm., and there remained a viscous yellow residue. A similar oxidation residue of average empirical composition corresponding nearly to $C_6H_{10}O_2$, and having P.O.C. 14·7%, and iod. val. 122, absorbed approximately 2 mols. of hydrogen in presence of Adams's catalyst, and then gave on distillation at 0·5 mm. pressure a little *cyclo*hexanol (10% yield), a little *cyclo*hexane-1 : 2-diol (1% yield), distillable "dimeric" materials ranging in b. p. from 60° to 120°, and an undistillable viscous residue. These high-boiling materials when reunited and extracted with hot water gave an extract (about $\frac{1}{3}$ of the total) which on redistillation at 0·5 mm. pressure gave almost equal fractions of b. p. (*a*) 84° and (*b*) 96° severally. These fractions had each approximately the empirical composition $C_6H_{10}O$ [Found: (*a*) C, 73·65; H, 10·2; (*b*) C, 72·15; H, 10·1. Calc. for $C_6H_{10}O$: C, 73·4; H, 10·3%].

A normal oxidation residue (9·8 g.) when immediately extracted with hot water gave an aqueous extract containing a pale yellow, acid syrup (3·5 g.), leaving an undissolved neutral yellow oil (A). This syrup was divided by the action of dilute alkali into a neutral (B) and an acidic portion (C). All these fractions were in the main distillable, but none boiled constantly. The neutral fraction (A) boiled principally between 80° and 90° at 1 mm., and varied somewhat in composition from fraction to fraction and from preparation to preparation

[*e.g.*, found for the main fractions of different peroxide-free preparations, (*a*) b. p. *ca.* 84°/1 mm., and (*b*) b. p. 80—86°/1 mm.: C, (*a*) 73·65, (*b*) 76·52; H, (*a*) 10·2, (*b*) 9·77. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·3%. $C_{12}H_{18}O$ requires C, 80·85; H, 10·2%]. The neutral, water-soluble fraction (B) had *M*, 320 (in benzene) and distilled for the most part at *ca.* 115°/13 mm. It was hygroscopic, reacted readily with benzoyl chloride, and was probably dihydroxylic (Found: C, 66·1; H, 9·9. $C_{12}H_{20}O_3$ requires C, 67·9; H, 8·5%). The hygroscopic, acidic, water-soluble fraction (C) had *M*, 231 (in benzene) and gave a main fraction of b. p. *ca.* 135°/13 mm. (Found: C, 56·7; H, 8·5%).

From 1-*Methylcyclohexene Hydroperoxide.*—The residue left when the hydroperoxide of 1-methylcyclohexene was distilled from the crude oxidation product (Found: C, 64·1; H, 9·0. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·4%) gave on extraction with water a neutral, water-insoluble oil and an acidic, water-soluble syrup. Both these materials were almost wholly distillable but heterogeneous, boiling over the ranges 110—128°/1 mm. and 74—108°/1 mm. respectively. These were not further examined.

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23. *The Course of Autoxidation Reactions in Polyisoprenes and Allied Compounds. Part II. Hydroperoxidic Structure and Chain Scission in Low-molecular Polyisoprenes.*

By ERNEST HAROLD FARMER and DONALD A. SUTTON.

The oxidation by molecular oxygen of three polyisoprene hydrocarbons, dihydromyrcene, dihydrofarnesene, and squalene, has been examined. Dihydrofarnesene, within the limits of observation (up to 6·0% of absorbed oxygen), becomes peroxidised to the full extent of the oxygen intake, but retains its original unsaturation: hence the peroxidic groups are ·OOH groups. Squalene and dihydromyrcene undergo extensive peroxidation, but almost from the beginning decay of the peroxide groups takes place side by side with peroxidation. Oxidised dihydromyrcene contains (*a*) oxygenated substances more or less peroxidic, and almost entirely monomeric, (*b*) oxygenated chain-scission products, and (*c*) untransformed peroxides of dihydromyrcene. Although the overall oxygen intake may be small, the stage of oxygenation reached in the molecules attacked may be well advanced, since distribution of the attack among the diolefinic molecules is uneven. The general nature of the oxygenated products and of the scission products has been investigated. From the complex oxygenated mixture there have been obtained by reduction of the peroxidic groups and subsequent fractionation hydroxydihydromyrcene, $C_{10}H_{17}(OH)$, possessing unimpaired the unsaturation of dihydromyrcene, and also (although in somewhat less pure form) dihydroxydihydromyrcene, $C_{10}H_{16}(OH)_2$.

The decrease of unsaturation in dihydromyrcene as it undergoes progressive oxidation is small compared with that which would take place if the absorbed oxygen became added at the double bonds (*e.g.*, to give cyclic peroxide groups $\overset{\cdot C \cdot C \cdot}{\underset{O \cdot O}{|\quad|}}$). During the decay of the peroxide groups the peroxidic oxygen becomes redistributed and enters at the unsaturated centres, which ultimately become the seats of chain scission. The loss of unsaturation produced by the entry of oxygen into those chains which remain unsevered is rather less than equivalent to the non-peroxidic oxygen (transformed peroxide) in the same undegraded chains, as estimated on the basis of two atoms of oxygen per double bond. The course of oxidation is indicated.

ONE of the most astonishing phenomena connected with the chemistry of rubber is the ease with which it absorbs progressively very small amounts of oxygen and suffers as a result drastic and progressive reduction of its molecular weight. The natural conclusion to be drawn is that the polyisoprene chains of the rubber are undergoing oxidative scission at one after another of their unsaturated centres, so that the original long hydrocarbon chains become divided into smaller and smaller fragments possessing oxygenated ends. Recent estimates of the molecular weight of rubber by viscosity and osmotic methods range from 240,000 to 360,000 for fractions of decreasing solubility in hydrocarbon solvents (Gee and Treloar, *Trans. Inst. Rubber Ind.*, 1941, **17**, 184; Bloomfield and Farmer, *ibid.*, 1940, **16**, 69). If we accept these figures and assume for the moment that two atoms of oxygen are sufficient to sever the hydrocarbon chains at a double bond, then an absorption of only 0·009—0·013% of oxygen (applied,

of course, exclusively to scission reactions) should suffice to reduce the average molecular weight to one-half. If the observed reductions of molecular weight are solely to be ascribed to oxidative scission of the chains, then, provided oxygen-consuming side reactions are few, a fairly exact inverse proportionality may be expected to hold between the uptake of oxygen and the average molecular weight of the degraded rubber. The most striking reductions in the molecular weight per unit of oxygen absorbed must, of course, occur at the very early stages of oxidative fission, while the hydrocarbon chains are still very long, and in order to be able to follow effectively the quantitative relationship between these important reductions and the oxygen uptake, it is necessary to make experimental provision for the absorption, even distribution, and measurement of very minute quantities of oxygen.* Minute though the overall proportion of oxygen necessary to produce a substantial reduction in molecular weight appears in practice to be, however, there is no evidence to indicate that the scission reaction ever follows the course most economical in oxygen, *i.e.*,

$$\cdot CMe{:}CH\cdot + O_2 \longrightarrow \cdot COMe + \cdot CHO$$

or indeed represents the sole, or even the most important, line of reaction among the secondary changes which follow the initial peroxidation of the hydrocarbon. The chains of greatly reduced molecular weight are still much too long to permit of any satisfactory direct examination of the individual products for the purpose of confirming the reality of the oxidative scissions or of determining the mechanism connecting the initial peroxides with (1) the scission products and (2) other secondary products (if any) comparable with the alcohols, epoxides, ketones, and dimerides formed from *cyclo*hexene and methyl-*cyclo*hexene (see Part I, preceding paper). For this reason, the autoxidative changes occurring in the low-molecular polyisoprenes, dihydromyrcene, dihydrofarnesene, and squalene, have been studied, and the present paper considers especially the character and point of entry of the peroxide groups, the tendency to chain scission, and the formation of oxygenated but unsevered chains.

The Formation and Character of Peroxide Groups.—The course of autoxidative reaction under ultra-violet irradiation which is shown by dihydromyrcene (I), dihydrofarnesene (II), and squalene (III)

(I.) $H\cdot[CH_2\cdot CMe{:}CH\cdot CH_2]_2\cdot H$ $\qquad$ $H\cdot[CH_2\cdot CMe{:}CH\cdot CH_2]_3\cdot H$ (II.)

(III.) $H\cdot[CH_2\cdot CMe{:}CH\cdot CH_2]_3\cdot[CH_2\cdot CH{:}CMe\cdot CH_2]_3\cdot H$

resembles in its primary aspects that pursued by various other olefinic substances. The absorbed oxygen forms peroxide groups, and these in lesser or greater degree decay, the peroxidic decompositions occurring side by side with the formation of new peroxide groups, so that the total content of peroxidic oxygen in the reaction mixture tends to fall seriously behind the oxygen intake. Small proportions of oxygen are lost by the formation of carbon dioxide and water, but these losses † are not very serious, especially in the early stages of reaction, so the peroxidic oxygen present at any moment represents some fraction, large or small, of the total oxygen in the system. The transformations of the peroxide groups, whether by isomerisation or by exercise of their energetic oxidative action on the rest of the molecule (or other molecules), constitute the chief autoxidative changes.

Now, in all studies of olefinic autoxidations described in the literature, the reasonably accurate measurement of the peroxide content in the unsaturated molecules and also that of the degree of unsaturation of the highly peroxidic products has been difficult and a source of error. The method of peroxide determination here employed is that referred to in Part I (p. 133), but special care has been necessary to avoid misleading values for the unsaturation of the peroxidised materials (see p. 145). In Fig. 1 the peroxide content is plotted against the oxygen content for dihydrofarnesene, dihydromyrcene, and squalene during the early stages of autoxidation. The behaviour of dihydrofarnesene is noteworthy in that all the absorbed oxygen up to an oxygen intake of 6·0% was found to be peroxidic and the hydrocarbon sustained no serious loss of unsaturation. The reaction mixture, therefore, contained at this point only unchanged hydrocarbon and dihydrofarnesene peroxides, and hence the latter could only have been of the hydroperoxide type. Dihydrofarnesene thus represented a very favourable example for the detailed examination of peroxidic structure, but owing to the great expense involved in the synthesis of the hydrocarbon (described elsewhere), no further study of the course of reaction could be undertaken. With squalene, absorption of oxygen up to 3·6% was observed. Here, the oxygen absorbed was found to be present entirely in peroxidic form at first, but decay of the peroxide soon set in, and at the end of the period of observation only about 57% of that formed had survived. The autoxidation product consisted

* Careful measurements of the relation between oxygen uptake and the diminution of the molecular weight in the earliest stages of oxidation have been undertaken by Dr. J. Bolland and will later be described.

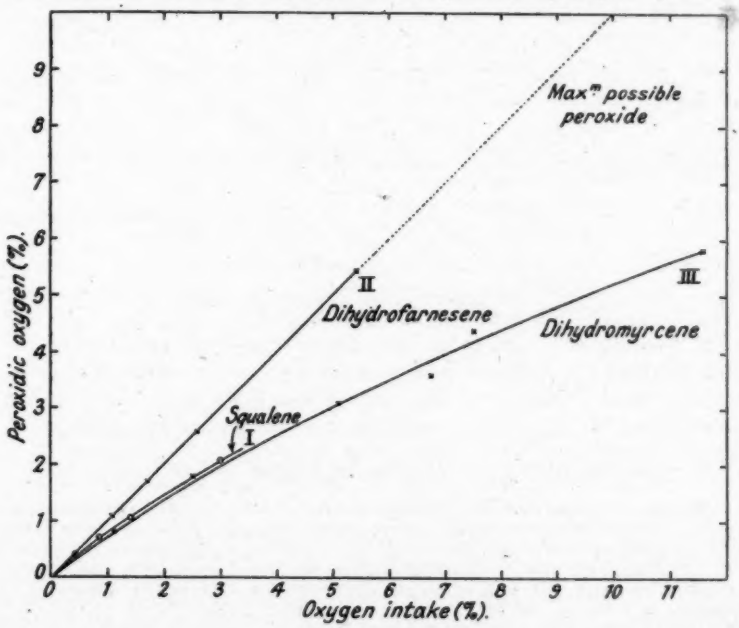
† Discussion of the significance of these is postponed, but owing to their low value the oxygen intake does not differ materially from the oxygen content as determined by analysis up to an advanced stage of reaction.

of unchanged hydrocarbon together with considerably oxygenated but largely non-peroxidic materials in which the original unsaturation had become very appreciably diminished. Autoxidation of dihydromyrcene was carried to an oxygen uptake of 11·6%, and of the peroxide thus formed only 50% survived in peroxidic form at the end of the period; repetitions of the oxidation gave very similar results. Since dihydromyrcene can be prepared with relative ease, it represents a convenient example for study.

General Character of the Autoxidation Products.—Pure dihydromyrcene (300 g.) was treated with oxygen in ultra-violet light (temperature 30—40°) for 45 hours, just over 7% by weight of oxygen being absorbed. About two-thirds of the hydrocarbon was found to have escaped oxidation, and of the remaining third about 4·5% consisted of relatively volatile scission products, and the residue of oxygenated dihydromyrcene possessed an *average* oxygen content of rather less than 25% (corresponding nearly to $C_{10}H_{18}O_3$). The scission products were distilled below 30° at 0·2 mm. pressure into a liquid-air trap, and the bulk of the unchanged hydrocarbon was driven over below 37° at the same pressure. The oxygenated residue was then fractionated below 70° by evaporative distillation at 10^{-3} mm. in a molecular batch still in an attempt to isolate some of the individual products.

FIG. 1.

Formation of Peroxide in Dihydrofarnesene, Squalene, and Dihydromyrcene.



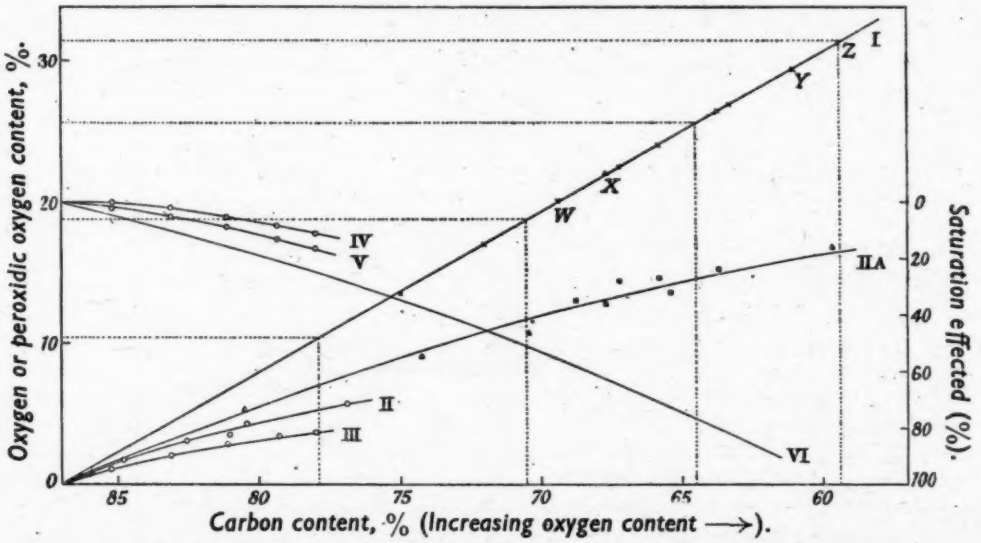
In general the moderate heating (below 45°) in high vacuum caused no very extensive damage to the peroxidised molecules. The peroxide contents of the less volatile portions were consistently high, and the unsaturation well marked. The active hydrogen values (dependent on both ·OOH and ·OH) were also very considerable, and tended to increase from the lower to the higher fractions, although there were considerable fluctuations from fraction to fraction. No satisfactory separation of the individual components of the mixture could, however, be effected. In order to improve the result if possible, refractionations of the more volatile distillates were carried out at 0·2 mm. pressure under a short column. The higher distillation temperatures, however, caused serious secondary change, so adding to the heterogeneity of the materials; and there was unmistakable evidence that very slow oxidative fission was occurring. Catalytic hydrogenation of the most promising fractions, followed by further fractional distillation under a column, did not give a homogeneous product.

In Fig. 2, Curve I, is shown the oxygen content, as determined by analysis, of a number of the fractions of undegraded oxygenated dihydromyrcene (selected over the range of oxygenation) plotted against the corresponding carbon content; the points *W*, *X*, *Y*, and *Z* on this curve, however, refer to the higher-boiling fractions of a second batch of oxidised dihydromyrcene. The oxygen values all fall with great precision on the oxygen content–carbon content curve (I) representing the formation of the oxidation stages $C_{10}H_{18}O$, $C_{10}H_{18}O_2$, $C_{10}H_{18}O_3$, $C_{10}H_{18}O_4$, from the hydrocarbon $C_{10}H_{18}$. All the distillate fractions

had remained unpolymerised, and thus each consisted of one or more materials belonging to these * oxidation stages, except for the very earliest ones (unrepresented in the diagram) which still contained some unchanged hydrocarbon. It is noteworthy that oxidation can advance as far as $C_{10}H_{18}O_4$ (and indeed the material of fraction *Z* actually had this empirical composition) in spite of the fact that by far the larger proportion of the available hydrocarbon molecules escaped reaction. This very uneven attack of the molecules submitted to the action of oxygen suggests, not only that the oxygen enters the chain not less than one molecule at a time, but that the entry of a peroxide group facilitates further attack in the same molecule; moreover, our observations indicate that such an uneven attack is by no means unusual in the autoxidative reactions of olefinic substances, and hence it is probable that many statements in the literature purporting to refer to the *early* stages of oxidation really refer to fairly advanced stages so far as the molecules actually attacked are concerned. *Prolonged* heating of the peroxidised materials at temperatures above 100° under reduced pressure caused not only redistribution

FIG. 2.

Oxidation of Dihydromyrcene.



Curve I: *Oxygen content of individual distilled fractions* (U.H.E.). Curve II: *Formation of peroxide in Oxidation No.* 1 (U.H.P.). Curve IIA: *Approximate peroxide content of the oxygenated hydrocarbon in Oxidation No.* 1 (U.H.E.). Curve III: *Formation of peroxide in Oxidation No.* 2 (U.H.P.). Curve IV: *Degree of saturation observed in Oxidation No.* 2 (U.H.P.). Curve V: *Degree of saturation in Oxidation No.* 2 *calculated from amount of non-peroxidic oxygen present in the reaction mixture on basis of* 1 *mol. of* O_2 *per double bond.* Curve VI: *Degree of saturation in Oxidation No.* 2 *which should be observed if* 1 *mol. of* O_2 *added to each double bond* (U.H.P.).

[U.H.E. = *Unchanged hydrocarbon eliminated from reaction mixture.* U.H.P. = *Unchanged hydrocarbon present in reaction mixture.*]

of oxygen, but some (low-molecular) polymerisation. Brownish-red, highly oxygenated, thermoplastic solids of trimeric or tetrameric complexity were so obtained.

The growth of peroxide groups in the hydrocarbon chains in comparison with the absorption of oxygen and the corresponding change in the unsaturation of the system deserves comment. The increase in the peroxide content (·O·O·) from stage to stage of a typical oxidation is shown for the undifferentiated mixture of unchanged and oxygenated hydrocarbon in curve II, Fig. 2. The same increase, but viewed in relation to just that portion (*i.e.*, about one-third) of the hydrocarbon which ultimately became successfully oxygenated, is shown approximately, for purposes of comparison with the oxygen intake (curve I), in curve IIA. The general level of the peroxide curve, however, varied materially from experiment to experiment in correspondence with small changes in the experimental conditions, and in Fig. 2 is shown a second peroxide-content curve (III) at a considerably lower level, that was obtained in a second

* Whether or no any oxygenated derivatives containing odd numbers of oxygen atoms are present must depend on the occurrence or otherwise of intermolecular reactions such as R·OOH + ·C:C· ⟶ R·OH + ·C·C·, and $R(OOH)_2$ + ·C:C· ⟶ R(OH)·OOH + ·C·C·.

experiment in which oxidation was accelerated (and the temperature of reaction raised a little) by attaching a reflector to the quartz lamp used previously. The content of non-peroxidic oxygen, as obtained by subtracting the ordinates of (II) or of (III) from those of (I), is seen through most of the reaction to amount to quite a large fraction of the total absorbed oxygen, showing that secondary reaction soon becomes an important feature of the oxidation.

Corresponding to the increasing degree of peroxide decay as the reaction proceeds, there is a progressive diminution in the unsaturation of the system. This diminution is shown for the second of the above experiments, where peroxide decay (see curve III) was considerably more severe than usual, by curve IV of Fig. 2, and it will be seen that the decrease is small compared with that which would have occurred if the absorbed oxygen had been progressively added at the double bonds (2 atoms per double bond) as represented in curve VI. The unsaturation of the system cannot therefore be affected by the *primary* oxidation reaction (*i.e.*, peroxidation), and hence the peroxide groups can hardly be other than hydroperoxide groups which, on entering the carbon chain, leave the original double bonds intact. It would be expected from the evidence of autoxidative tendencies described in Part I that the degree of double-bond saturation brought about by the oxidation (cf. curve IV) would tend to show a quantitative correspondence with the non-peroxidic oxygen appearing in the reaction, on the basis of 2 atoms of non-peroxidic oxygen present per double bond lost * (curve V), since the important paths of decomposition open to the hydroperoxide groups all appear to involve concomitant oxidative saturation of a double bond rather than direct disintegration of the groups to leave the double bond intact [*e.g.*, as would occur if the decomposition $R{\cdot}CH(OOH){\cdot}CH{:}CH{\cdot} \longrightarrow R{\cdot}CO{\cdot}CH{:}CH{\cdot} + H_2O$ were involved]. The occurrence of advanced stages of oxidation leading to chain scission and beyond, would, however, diminish the degree of this correspondence, since peroxidic oxidising power would then be used for post-saturation purposes. Experimentally, it was found that the degree of saturation effected did not reach equality with that to be expected on the basis of the non-peroxidic oxygen present, but amounted to about two-thirds of this (see curve V). Doubtless the appearance of chain-scission products from an early stage of the oxidation adequately accounts for the difference.

The Peroxidic Constitution.—In the case of peroxidised dihydrofarnesene (above), which suffered over the range of our observation no serious loss of unsaturation, reduction of the peroxide groups present would be expected to lead to the formation of a mixture of hydroxy- and dihydroxy-dihydrofarnesene [$R{\cdot}OOH + 2H \longrightarrow R{\cdot}OH + H_2O$; $R'(OOH)_2 + 4H \longrightarrow R'(OH)_2 + 2H_2O$]. If the peroxide groups in oxidised dihydromyrcene are similarly of hydroperoxidic character, as appears from the foregoing evidence to be the case, then those peroxidised molecules which have escaped secondary change, both in the actual oxidation and in any subsequent operations, should yield hydroxy- and dihydroxy-dihydromyrcenes on reduction, the former doubtless having one or other of the formulæ (A), (B), and (C), and the latter one or the other of (D) and (E) (see Part I), or alternatively either compound being a mixture of the appropriate isomerides.

$$CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH(OOH){\cdot}CMe{:}CH{\cdot}CH_3 \longrightarrow CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH(OH){\cdot}CMe{:}CH{\cdot}CH_3 \quad (A)$$

$$CH_2(OOH){\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_3 \longrightarrow CH_2(OH){\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_3 \quad (B)$$

$$CH_3{\cdot}CMe{:}CH{\cdot}CH(OOH){\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_3 \longrightarrow CH_3{\cdot}CMe{:}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_3 \quad (C)$$

$$CH_2(OOH){\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH(OOH){\cdot}CMe{:}CH{\cdot}CH_3 \longrightarrow CH_2(OH){\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH(OH){\cdot}CMe{:}CH_2{\cdot}CH_3 \quad (D)$$

$$CH_3{\cdot}CMe{:}CH{\cdot}CH(OOH){\cdot}CH(OOH){\cdot}CMe{:}CH{\cdot}CH_3 \longrightarrow CH_3{\cdot}CMe{:}CH{\cdot}CH(OH){\cdot}CH(OH){\cdot}CMe{:}CH{\cdot}CH_3 \quad (E)$$

Since in all our oxidations of dihydromyrcene a very considerable proportion of the peroxide groups always underwent secondary change during the oxidation itself, it was inevitable that any reduction products of the type (A)—(E), and especially dihydroxy-products such as (D) and (E), would be found in the reduced product mixed with other oxygenated materials of very similar empirical composition. Hence, separation of pure products would be difficult, and the yields of such separated materials poor. In practice, aluminium amalgam proved to be an effective reducing agent, but the low yield of hydroxy-dihydromyrcene to be expected was still further diminished owing to the difficulty experienced in recovering the alcoholic product completely from the alumina formed. Nevertheless, a monohydric alcohol, $C_{10}H_{17}{\cdot}OH$, having two double bonds and one atom of active hydrogen per molecule, was duly isolated by fractional distillation, and also a corresponding dihydric alcohol, $C_{10}H_{16}(OH)_2$. The former was with little doubt (A) or (C) or a mixture of both; the latter, however, on the scale of experimentation open to us, could not be freed entirely from more highly oxygenated materials of similar boiling point, and so the final fractionation product, although showing the correct active hydrogen content, had a somewhat low degree of unsaturation ($I_{I_2}^{=}$) and a rather too high oxygen content. Repetition of the reduction with a further batch of oxidised dihydromyrcene gave exactly similar results. It is of some

* Compare equations (A), (D), and (E), Part I.

interest that the somewhat heterogeneous dihydric alcohol reacted readily and nearly quantitatively with standard lead tetra-acetate solution, and hence appears according to Criegee's rule to have consisted almost completely of α-glycols: therefore the major product is likely to have been (E) rather than (D), and the minor, more highly oxygenated component, a mono-olefinic triol such as $CH_3{\cdot}CMe(OH){\cdot}CH(OH){\cdot}CH_2{\cdot}CH(OH){\cdot}CMe{:}CH{\cdot}CH_3$ or $CH_3{\cdot}CMe{:}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}CMe(OH){\cdot}CH(OH){\cdot}CH_3$.

The Products of Chain Scission.—The observations recorded in Part I indicate clearly that redistribution of the active oxygen of the hydroperoxide groups occurs largely or entirely as the direct result of the energetic oxidising action of the latter. In the absence of other reactive centres (*e.g.*, >CO, $\cdot C\overset{\diagdown}{\underset{\diagup}{C}}\cdot$ the chief oxidative attack occurs at the olefinic centres, and these accordingly first become saturated by oxygenation and ultimately, if reaction goes far enough, become the seats of chain scission. Two different types of scission reaction are to be distinguished, *viz.*, (*a*) in which break occurs at the double bond without any oxygenation of the α-carbon atoms, and (*b*) in which break occurs at the double bond but one or other of the α-carbon atoms becomes oxygenated and subsequently, if reaction goes far enough, split off. The first of these is initiated by an external peroxide or peracid group

$$R{\cdot}OOH + {\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot} \longrightarrow R{\cdot}OH + {\cdot}CH_2{\cdot}\underset{\diagdown\ \diagup}{CMe{\cdot}CH}{\cdot}CH_2{\cdot}$$
$$\qquad\qquad\qquad

(2) In this primary reaction the unsaturation of the system remains unaffected.

(3) Secondary autoxidative changes, spontaneous or promoted by heat or other influences, set in with different degrees of facility in different substances and consist largely in the interaction of the hydroperoxide groups at the double bonds, which results mainly in oxidatively saturating the latter without severing them, although in a proportion of molecules reaction goes far enough to cause scission.

(4) In many substances the secondary reactions begin almost at the outset of reaction and proceed side by side with further peroxidation. The entry of oxygen into a molecule appears to facilitate further autoxidative attack in the same molecule, so that a low overall oxygen intake is compatible with advanced oxidation in some of the molecules.

(5) Reduction of the peroxide groups in those peroxidised dihydromyrcene molecules which have escaped secondary reaction yields alcohols which retain intact the original unsaturation of the hydrocarbon.

(6) Chain scission takes place with some facility at the double bonds, with formation of fragments with oxygenated ends, but subsidiary scission appears to occur also at certain of the single bonds adjacent to the double bonds.

Experimental.

Dihydromyrcene.—Myrcene was prepared from bay oil (*Pimenta acris*) by the method of Power and Kleber (*Pharm. Rundschau*, 1895, **13**, 60). The well-washed hydrocarbon, fractionated over sodium, had b. p. 51—53°/10 mm., $d_4^{20°}$ 0·7981, $n_D^{22°}$ 1·468, and gave at once with maleic anhydride the adduct, m. p. 34° (Diels, m. p. 34—35°), and the latter by hydrolysis the corresponding dicarboxylic acid, m. p. 122° (Diels, m. p. 122—123°). Yield, 20% of original oil. The myrcene was reduced with sodium and alcohol as described by Semmler and Mayer (*Ber.*, 1911, **44**, 2010), except that 162 g. of sodium and a total of 1820 c.c. of absolute alcohol per 500 g. of hydrocarbon sufficed to ensure complete reduction. The well-washed hydrocarbon, after being twice distilled over sodium through a Widmer column, boiled at 52·5—55°/11 mm. (Found: C, 86·8; H, 13·1. Calc. for $C_{10}H_{18}$: C, 86·9; H, 13·1%). It had $d_4^{20°}$ 0·7809, $n_D^{23°}$ 1·4495, and gave a tetrabromide, m. p. 87—88° (Found: Br, 69·8. Calc.: Br, 69·8%). Semmler and Mayer report $d_4^{15°}$ 0·7802, $n_D^{20°}$ 1·4507 and m. p. of tetrabromide, 87°. To ensure that the dihydromyrcene contained no myrcene, a portion (10 g.) was heated at 100° for 10 mins. with maleic anhydride. No visible reaction occurred, no trace of adduct could be found, and the recovered hydrocarbon had the original physical constants.

Squalene.—A fraction of the liver oil of *Symnorhinus lichia* of b. p. 225—235°/1 mm. was used, after it had been well washed with caustic alkali and with water. This pale yellow hydrocarbon contained oxygenated impurities as Heilbron *et al.* had observed (J., 1926, 1630) with similar specimens, but these were expeditiously and satisfactorily removed by adsorption on activated alumina (21 g. of hydrocarbon dissolved in 1000 c.c. of light petroleum run slowly through a column of alumina 33 cm. × 2 cm., and the chromatogram developed by 150 c.c. of light petroleum). The purified oil (Found: C, 87·8; H, 12·3. Calc. for $C_{30}H_{50}$: C, 87·7; H, 12·3%) had $d_4^{20°}$ 0·8562, $n_D^{23°}$ 1·494, $[R_L]_D$ 139·5, and showed like Heilbron's product an appreciable molecular exaltation (1·5 units). The cause of this exaltation will be considered in a later paper.

Dihydrofarnesene.—This tri-isoprene was synthesised from geraniol as will be described later.

Determination of Unsaturation.—For the determination of unsaturation in oxidised polyisoprenes the iodine-value method is convenient but has the disadvantage that organic peroxides react with the potassium iodide used as reagent, and by liberating iodine cause low unsaturation values to be obtained. Direct hydrogenation is an alternative, but owing to the necessity of determining the peroxide content separately and subtracting the hydrogen equivalent of the peroxide ($R{\cdot}OOH + H_2 \longrightarrow R{\cdot}OH + H_2O$) from the total quantity of hydrogen absorbed, the method is subject to a double error, which renders it too inaccurate for use with small quantities of material, although it enables very useful near approximations to be made with specimens of several g. or more. Determination of unsaturation by bromine addition has proved unsatisfactory, and determination by means of standard solutions of peracids is unsuitable owing to the tendency of these oxidising agents to cause chain scission with consumption of additional peroxide. Of all these methods, as conducted under various recommended procedures, the iodine value has proved to be most satisfactory for general analytical control, but the magnitude of the error even under standard conditions of working is variable owing to differences in the reducibility of different peroxides. For the reactive hydroperoxides of low-molecular polyisoprenes and *cyclo*hexene peroxides, unsaturation values found by the iodine value method are estimated to be 4—5% too low, but not more, provided the final titration after the addition of potassium iodide be conducted rapidly, and in a solution well diluted with water. The existence of this error renders the direct observation of very small changes in unsaturation in the early stages of peroxidation (*e.g.*, in the case of dihydrofarnesene) unreliable. The unsaturation values used in plotting curves (IV)—(VI), Fig. 2, are uncorrected ones, and hence the degrees of saturation there shown are considered to be about 5% higher than the actual value.

General Oxidation Procedure.—The unsaturated hydrocarbon, together with a diluent if desired, was placed in a 2-necked Pyrex flask and connected through a calcium chloride tube to a gas burette and reservoir containing oxygen. The air in the flask was displaced with oxygen, and the flask placed 15 cm. from an ultra-violet lamp (Hanovia U.V.S. 500) and shaken mechanically. The heat radiated from the lamp kept the flask at a

temperature between 35° and 40°. Usually after an induction period of about 1 hr. absorption of oxygen began and was allowed to proceed until the desired amount of oxygen had been absorbed, or until absorption seriously slackened. For determination of the peroxide formed, or the saturation effected from stage to stage in the oxidation, suitable portions of material were withdrawn with a pipette through one of the necks of the flask, the level of the gas burette being noted before and after the interruption, and the air unavoidably admitted to the flask during the interruption being replaced by oxygen before oxidation was continued. Invariably in the course of the oxidation a little water was eliminated, and some carbon dioxide formed. Since neither of these up to the point of oxidation desired interfered with the absorption of oxygen or caused any very serious error in the measurement of the oxygen intake (as confirmed by numerous comparisons of the latter with the oxygen content of the products), no steps were taken to remove them as they were formed.

Oxidation of Squalene.—The purified squalene (10 c.c.; 8·45 g.), dissolved in 100 c.c. of pure dry benzene, was oxidised at 35—40° for 105 mins. after the induction period (60 mins.) had ended. Withdrawals of 2 c.c. of the solution were made from time to time, and the peroxide content of each sample determined. The change in the peroxide content of the solution of hydrocarbon up to an average oxygen intake of 3·6% of its weight is shown in Fig. 1, curve I. The product was freed from solvent by distillation of the latter at reduced pressure, and the residual oil (7·6 g.) was divided into two parts by fractional dissolution in methyl alcohol. The alcohol-insoluble portion (5·5 g.) was nearly free from oxygen [Found: C, 87·2; H, 12·3; O (by diff.), 0·5. Calc. for $C_{30}H_{50}$: C, 87·7; H, 12·3%] and consisted mainly of unchanged squalene, whilst the alcohol-soluble portion consisted of oxygenated squalene having an average empirical composition of $C_{30}H_{50}O_{3\cdot65}$, and a peroxide content (6·5%) slightly more than half the total average oxygen content.

Oxidation of Dihydrofarnesene.—This triene hydrocarbon (4·14 g.) was oxidised without a diluent, withdrawals of samples (3) being made at intervals as before. The hydrocarbon, which had been kept in a stoppered bottle for 1 week after purification, contained at the outset 0·22% of peroxidic oxygen, and finally after absorption of 6·0% of its weight of oxygen (leading to an average empirical formula of $C_{15}H_{26}O_{0\cdot82}$) contained 6·0% of peroxidic oxygen. The unsaturation, determined by iodine values, diminished inappreciably, and had finally decreased by 4·8% (<0·8% corrected) of the initial figure.

Oxidation of Dihydromyrcene.—Dihydromyrcene (100 g.) was oxidised without a diluent during 42½ hours, samples being withdrawn at intervals for peroxide determination. The total oxygen intake amounted to 11·6% of the weight of hydrocarbon taken. The variation of the peroxide content as the absorption of oxygen proceeded is shown in Fig. 1, curve III.

A further quantity of hydrocarbon (300 g.) was oxidised as before, absorption of oxygen being continued until it became slow. A total of 16,550 c.c. of oxygen was absorbed in 45 hours. The product (nearly 323 g.) was placed in a 2-necked flask surmounted by a Widmer column and connected to a liquid-air trap. The flask was very gently warmed at 0·2 mm. pressure to drive over (i) very volatile products (*A*) which collected in the liquid-air trap (27·6 g.), (ii) volatile materials (*B*) of b. p. 30—37° (205 g.), leaving (iii) a residue (*C*) (85 g.) in the flask.

The fraction (*A*) evolved no gases when it was warmed slowly up to 10°, and it could be distilled at atmospheric pressure under a short Vigreux column without great loss of volatile matter. There were obtained (*a*) acetaldehyde (dimedon derivative, m. p. 140—141°; mixed m. p. 140—141°. Found: C, 70·5; H, 8·5. Calc. for $C_{18}H_{26}O_4$: C, 70·55; H, 8·55%), (*b*) a volatile liquid, b. p. 30—74°, which yielded on refractionation more acetaldehyde, a quantity of acetone (2 : 4-dinitrophenylhydrazone, m. p. 126°; mixed m. p. 126°. Found: N, 23·9. Calc. for $C_9H_{10}O_4N_4$: N, 23·5%), (*c*) a fraction, b. p. 60—90°, which separated into two layers and on refractionation gave water, some acetic acid (*p*-bromophenacyl ester, m. p. 84°; mixed m. p. 85°. Found: C, 46·35; H, 3·6; Br, 31·65. Calc. for $C_{10}H_9O_3Br$: C, 46·7; H, 3·5; Br, 31·1%), a small amount of pungent volatile acid of b. p. *ca.* 100°, which satisfied Rimini's and other qualitative tests for formic acid, and a quantity of unidentified volatile liquid material, and (*d*) 22 g. of crude hydrocarbon [added to (*B*)]. The total yield of the volatile scission products including acetaldehyde, acetic acid, water, and acetone and unidentified products amounted to 4·5—8% of the weight of hydrocarbon actually oxygenated (*ca.* 100 g.).

The fraction (*B*) (205 g. + 22 g.) was found on refractionation to consist almost entirely of unchanged dihydromyrcene, but it contained some non-ketonic oxygenated material. The total proportion of unchanged dihydromyrcene, including the first of the sub-fractions of (*C*, I) (see below) was estimated to be 200 g.

The fraction (*C*) was a light yellow, fairly mobile oil of strong peroxidic character (peroxidic oxygen, 9·62%) which was first partly distilled at 10^{-3} mm. pressure in a batch still, the most volatile portion, (*C*, I) (16·65 g.; peroxidic oxygen, 0·94%), being collected in a liquid-air trap, the intermediate portion (*C*, II) (29·7 g.; peroxidic oxygen, 12·9%) distilling at 60—70° as a slightly viscous, yellowish oil, leaving a residue (*C*, III) (25·85 g.; peroxidic oxygen, 12·2%) of yellow viscous liquid.

The fraction (*C*, I) was divided by fractional distillation under a short column into 5 fractions ranging in b. p. from 56° to 104°/12 mm. The first (2 g.) consisted of dihydromyrcene, the second, containing only 6·05% of oxygen, was of rather lower unsaturation than dihydromyrcene (179·8 g. equiv. to $2I_2$) and consisted of dihydromyrcene mixed with an oxygenated substance which appeared to be an alcohol (? tertiary) since it reacted with 3 : 5-dinitrobenzoyl chloride to give a red oil, which in turn gave a thick red oil with α-naphthylamine. The third was acidic, containing a little formic acid which had been produced by thermal

degradation during the distillation; when the formic acid was removed, the highly oxygenated residue had barely half the unsaturation of dihydromyrcene (148·6 g. equiv. to I_2) and was non-ketonic [Found: C, 75·0; H, 11·55; O (by diff.), 13·45%]. The fourth fraction was also non-ketonic but was more highly oxygenated than the third and slightly more unsaturated [Found: C, 72·0, 72·05; H, 10·65, 10·9; O (by diff.), 17·35, 17·05%; 138·7 g. equiv. to I_2]. The fifth (1·1 g.), which was very viscous and apparently somewhat polymerised by heat, was discarded.

A portion (18 g.) of the fraction (*C*, II) was divided by fractional distillation at 10^{-3} mm. pressure in the batch still into five portions (*C*, II, *a*—*e*), four of which were distillates ranging in b. p. from 40° to 50°, and the fifth the residue. The following data were obtained: *C*, II*a*: C, 65·85; H, 9·85; O (by diff.), 24·3; O (peroxidic), 11·7; active H, 0·62%; *C*, II*b*: O (peroxidic), 11·7%; *C*, II*c*: C, 67·2; H, 10·2; O (by diff.), 22·6; O (peroxidic), 14·6; active H, 0·74%; *C*, II*d*: C, 63·7; H, 9·8; O (by diff.), 26·5; O (peroxidic), 15·5%; *C*, II*e*: C, 63·65; H, 9·5; O (by diff.), 26·85%. A little volatile material (1·2 g.) of low peroxidic content (1·6%) also collected in the liquid-air trap.

Of the above fractions *C*, II*c* was reduced catalytically by means of Adams's catalyst, which was removed by centrifuging. The saturated and peroxide-free product was divided by fractional distillation into 6 fractions (i—vi). Of these (i), b. p. 82—85°/12 mm. (0·15 g.), closely resembled (ii) and was not separately examined; (ii) was a sweet-smelling oil, b. p. 86—90°/12 mm. (Found: C, 73·0; H, 12·95%), which reacted with 3 : 5-dinitrobenzoyl chloride to give a red oil, but this gave no solid adduct with α-naphthylamine (cf. Reichstein, *Helv. Chim. Acta*, 1926, **9**, 799); (iii) was a nearly odourless oil, b. p. 96—98°/12 mm. [Found: C, 72·6; H, 12·7; O (by diff.), 14·7%], which probably contained as minor component an alcohol of formula $C_{10}H_{22}O$, since it reacted with 3 : 5-dinitrobenzoyl chloride to give a red oil, forming with α-naphthylamine a somewhat unstable and difficultly crystallisable *derivative*, m. p. 91—96° (15% yield) (Found: N, 8·8. $C_{17}H_{24}O_6N_2,C_{10}H_9N$ requires N, 8·9%), but since its oxygen content greatly exceeds that of hydroxydihydromyrcene (O, 10·4%) which has approximately the same b. p., the major component must contain together with hydroxyl a volatile oxygen-containing group such as epoxy; (iv) was an odourless oil, b. p. 104—114°/12 mm. (Found: C, 70·95; H, 11·95%); (v) was a viscous oil, b. p. 117—122°/12 mm., of high oxygen content and hydroxylic character which probably consisted mainly of dihydric alcohol, $C_{10}H_{22}O_2$, and in part of an α-glycol, since about half of it reacted with lead tetra-acetate (Found: C, 68·4; H, 11·55. Calc. for $C_{10}H_{22}O_2$: C, 68·96; H, 12·6%).

The residue (*C*, III) remaining in the still was a pale yellow syrup of average composition $C_{10}H_{18}O_{2\cdot2}$ (see p. 141) and peroxide content 12·2% (*i.e.*, an average of 0·71 ·OOH group per mol.). A portion (14·3 g.) was hydrogenated in presence of Adams's catalyst, and the saturated hydroxylic products were divided into ten portions by fractional distillation, leaving a tiny residue. All fractions were yellow oils, and the 4 lowest ones, b. p. 40—110°/10 mm., resembled those derived by hydrogenation of fraction (*C*, II*c*) above; the higher ones, *C*, III, vii—ix, b. p. 75—146°/1 mm., all had the empirical composition $C_{10}H_{19\cdot8}O_{2\cdot5}$, and the highest (*C*, III, x) and the residue had the composition $C_{10}H_{18\cdot5}O_{2\cdot8}$ and $C_{10}H_{17\cdot5}O_{3\cdot16}$ respectively. It is to be deduced, therefore, that the sub-fractions vii—ix have taken up an average of 1·8 atoms of hydrogen and lost 0·7 atom of oxygen per mol., and hence the peroxidic parent material must have contained an average of 0·9 and *ca.* 0·7 ·OOH group per mol. The final fractions (x and residue), however, have respectively gained $H_{0\cdot5}$ and lost $H_{0\cdot5}$ per mol. and respectively lost $O_{1\cdot0}$ and $O_{0\cdot95}$ per mol. This doubtless marks the beginnings of the post-saturation autoxidative changes leading to chain scission and its accompaniments of water and carbon dioxide elimination, and in the residue possibly of polymerisation.

Advanced Stage of Oxidation.—Oxidation of 100 g. of dihydromyrcene gave after exhaustive distillation of the less oxygenated fractions at reduced pressures and at bath temperatures below 100° a residue in the still having a composition of nearly $C_{10}H_{18}O_4$ and containing 11% of peroxidic oxygen [Found: C, 59·7: H, 9·0; O (by diff.), 31·3. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0; O, 31·6%]. In another oxidation of hydrocarbon the final fraction obtained by distillation had an empirical formula of nearly $C_{10}H_{18}O_{3\cdot7}$ [Found: C, 61·0; H, 9·1; O (by diff.), 29·9%] and peroxidic oxygen 15·1%.

Action of Prolonged Heating.—The oxidation product from 29 g. of dihydromyrcene (7·1% oxygen intake) was freed from unchanged hydrocarbon, and fractionally distilled at successive pressures of 13 mm., 1—2 mm., and 10^{-3} mm., the temperature of the heating bath being allowed to rise to about 150° in each case. The residue in the still (*ca.* 5 g.) formed a brownish-red, resinous mass, which was extensible on warming, and able to yield fine threads. It had approximately the composition $C_{10}H_{18}O_2$, and from cryoscopic determinations had between tri- and tetra-meric complexity [Found: C, 70·2; H, 9·3; O (by diff.), 20·5%; *M* (in benzene), 610. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6; O, 18·8%; *M*, 170]. The polymerisation process had thus involved material loss of both hydrogen and oxygen, probably largely as water.

Reduction of Hydroperoxido- and Dihydroperoxido-dihydromyrcene.—Dihydromyrcene (300 g.) was oxidised in a quartz flask to an oxygen intake of only 1%, and then immediately reduced by aluminium amalgam in moist ether containing a little alcohol. Reaction was vigorous at first, and after 24 hours all peroxidic material had disappeared. The ethereal solution, freed from alumina and from the large bulk of unchanged dihydromyrcene, gave only a moderate yield of reduced product, which by re-extraction of the alumina was finally raised to 60% of that expected. Since extensive secondary autoxidation processes unavoidably accompany peroxidation, it was necessary to select the desired products by careful fractional distillation,

Fractions were finally obtained of b. p. (i) 55—58°/12 mm. (1·7 g.), (ii) 58—83°/12 mm. (0·9 g.), (iii) 90—103°/12 mm. or 70—76°/1 mm. (1·8 g.), (iv) 80—96°/1 mm. (0·1 g.), (v) 96—106°/1 mm. (0·5 g.), (vi) 115°/1 mm. (0·5 g.), and (vii) residue (1 g.). The fractions (i) and (ii) both contained some dihydromyrcene, but (iii) was free from hydrocarbon and had the correct composition and characteristics for *hydroxydihydromyrcene* (Found: C, 77·75; H, 11·35; active H, 0·65; $|\overline{=}_{1\cdot98}$. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7; active H, 0·65%; $|\overline{=}_{2\cdot0}$). The alcohol reacted with 3 : 5-dinitrobenzoyl chloride to give a thick red oil, affording a non-crystalline complex with α-naphthylamine.

The fraction (iii) approximated in composition and characteristics to *dihydroxydihydromyrcene* (Found: C, 68·85; H, 10·45; active H, 1·05; $|\overline{=}_{1\cdot6}$. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6; active H, 1·18%; $|\overline{=}_{2\cdot0}$), but clearly contained a little more highly oxygenated material. The diol reacted with N/10-lead tetra-acetate (Consumption: 96·5% of theory) and probably consists mainly of a 1 : 2-diol of formula (E) (p. 143).

The above work has been carried out as part of the programme of fundamental research on rubber undertaken by the Board of the British Rubber Producers' Research Association.

THE BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
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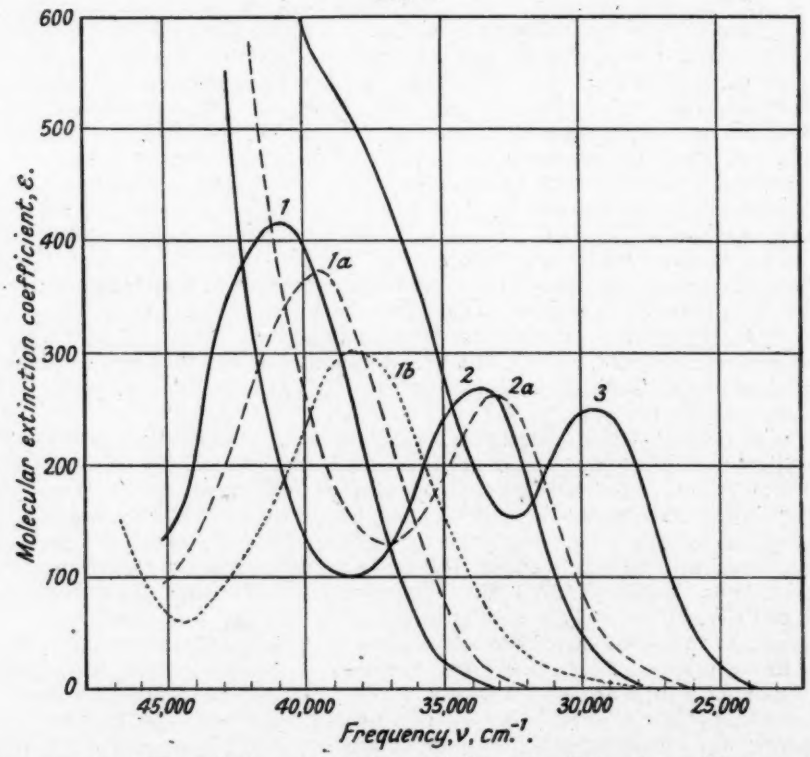
24. *The Absorption Spectra of Mono-, Di-, and Tri-chloroamines and Some Aliphatic Derivatives.*

By W. S. METCALF.

The chloroamines examined show a characteristic absorption band lying between the limits $\nu_{max.} = 40800$ cm.$^{-1}$, $\varepsilon_{max.} = 416$, and $\nu_{max.} = 29400$ cm.$^{-1}$, $\varepsilon_{max.} = 255$. The less the polarisability of the groups attached to the >N–Cl chromophore, the greater is the frequency of maximum absorption.

IN view of the fact that most chloroamines are unstable and sensitive to light, their spectra were examined in aqueous solution, which was circulated through the absorption cell of a sector photometer attached to a

FIG. 1.



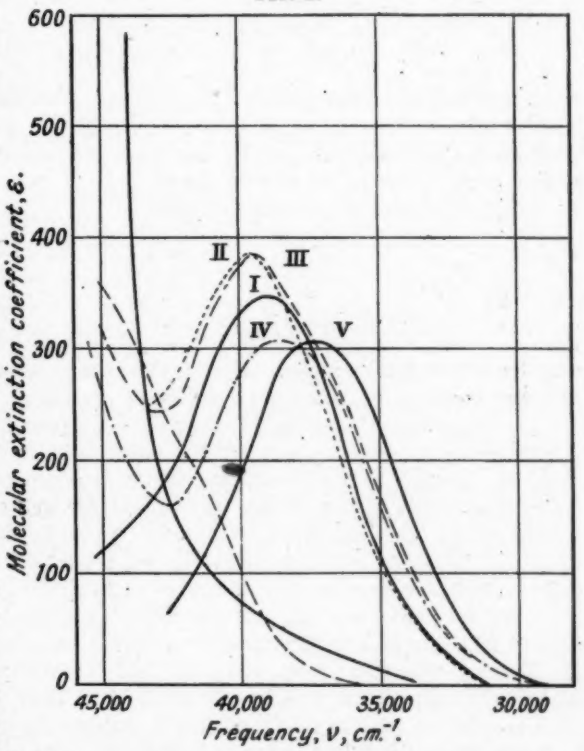
small quartz spectrograph. The solution passed through the cell sufficiently rapidly to prevent appreciable photochemical decomposition.

In order to keep a constant check on the concentration of the solution, it was collected after circulation in a device arranged to deliver aliquot portions. These were run into an acidified solution of potassium iodide and the iodine liberated was titrated with 0·01N-sodium thiosulphate.

The chloroamine solutions were obtained by adding hypochlorous acid to a solution of the appropriate amine buffered with acetate or phosphate mixtures. These buffered solutions gave an improved yield of chloroamine, and a more stable solution. The substances chosen for the buffer are stable to chlorine and sufficiently transparent to ultra-violet light.

The concentration of chloroamine as measured by titration falls on standing, but the molecular extinction coefficient $\varepsilon = (1/cd) \log I_0/I$ was found not to vary as the solution decomposed, provided that the value of c was taken as the concentration of chloroamine measured by titration. This proves that products formed by the decomposition of chloroamines have a negligible effect on the absorption spectra of the solutions. Deviations were observed in solutions whose titre had fallen to half the original value, but such solutions were not used for measurements. The yield of chloroamine obtained on mixing the amine with hypochlorous acid was always greater than 90% of the theoretical.

FIG. 2.



Solutions of hypochlorous acid and ammonia show the spectrum of hypochlorite ions at p_H greater than 14, of chloroamine over the range 14—7·5, of dichloroamine from 5·5 to 3, and of nitrogen trichloride at p_H less than 2·8. This equilibrium and those of other amines are now being studied. The spectra are quite constant over a range of p_H. Chapin (*J. Amer. Chem. Soc.*, 1929, **51**, 2113), by extraction with chloroform, has isolated the chloroamines formed at various hydrogen-ion concentrations, and has confirmed their identity analytically. Similarly, methylchloroamine is prepared in 0·1N-alkali, whereas methyldichloroamine is obtained in a solution buffered at p_H 7.

All other chloroamines were prepared in solutions buffered at p_H 7, save *N*-chloroacetamide which was prepared as pure crystals and dissolved in water.

The values of the wave-length, frequency, and molecular extinction coefficient are listed in the table. Fig. 1 shows the absorption curves for the alkyl-substituted chloroamines, and Fig. 2 those of more complex chloroamines, which show only minor differences from the spectra of the corresponding alkyl compounds. Methyl, ethyl, and *n*-propyl derivatives have spectra identical within the experimental error.

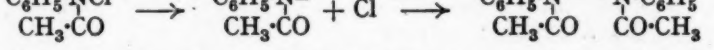
	$\lambda_{max.}$, A.	$\nu_{max.}$, cm.$^{-1}$.	$\epsilon_{max.}$	Fig.*
Chloroamine	2450	40,800	416	1
Monosubstituted chloroamines:				
Methylchloroamine	2530	39,500	372	1*a*
N-Chloroglycine	2560	39,100	350	I
N-Chloroalanine	2530	39,500	385	II
N-Chloroaspartic acid	2540	39,400	380	III
Disubstituted chloroamines:				
Dimethylchloroamine	2630	38,000	300	1*b*
Diethylchloroamine	2630	38,000	300	1*b*
Di-*n*-propylchloroamine	2630	38,000	300	1*b*
N-Chloromorpholine	2600	38,500	312	IV
N-Chlorosarcosine	2680	37,300	310	V
Dichloroamine	2970	33,700	265	2
Monosubstituted dichloroamines:				
Methyldichloroamine	3030	33,000	260	2*a*
Ethyldichloroamine	3030	33,000	260	2*a*
Trichloroamine:				
(Nitrogen trichloride)	3400	29,400	255	3

* Arabic numerals refer to Fig. 1 and Roman numerals to Fig. 2.

Discussion.—The frequencies of the maxima lie in groups corresponding to the number and type of the atoms attached to the >NCl chromophore. In order of decreasing frequency (and also, incidentally, of decreasing intensity) these groups are: chloroamine, alkylchloroamines, dialkylchloroamines, and trichloroamine (nitrogen trichloride). A carbonyl group adjacent to the nitrogen atom of the >NCl chromophore removes selective absorption from the region studied. If, however, the carbonyl group is separated by a carbon atom from the chromophore as in *N*-chloroglycine, the spectrum is little different from that of the corresponding alkylchloroamine.

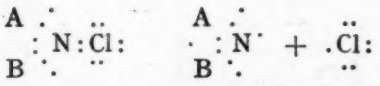
The frequencies of the maxima are in the inverse order of the polarisabilities of the groups –H, $-CH_3$, –Cl (cf. Ingold, *Chem. Rev.*, 1939, **15**, 255) attached to the chromophore.

From the work of Hodges (J., 1933, 240), who has shown that diacetylhydrazobenzene is formed in the photochemical decomposition of *N*-chloroacetanilide, thus:



it is probable that the absorption of ultra-violet light by chloroamines results in the disruption of the >NCl bond. Price (*Ann. Reports*, 1939, **36**, 58) considers that absorption in the near ultra-violet by polyatomic molecules is usually due to a transition from a bonding to an antibonding orbital causing disruption in the case of a single bond.

If we represent this disruption thus,



then the more the groups A and B are able to provide electrons to the nitrogen atom, the more readily will dissociation take place. Hence, the energy required for the dissociation is less, and light is absorbed at lower frequencies, the more polarisable are the groups attached to the chromophore.

The attraction of the carbonyl group for electrons may also account for the removal of absorption to the extreme ultra-violet region in the cases of *N*-chloroacetamide and *N*-chloroacetylglycine, although in these spectra the characteristic maximum was not observed.

Similar shifts in the spectra of water, hydrogen sulphide, and ammonia have been observed on alkyl substitution. In these instances the spectra lie at higher frequencies and dissociation does not necessarily occur. Price (*loc. cit.*) considers the shift here to be due to accumulation of negative charge on the oxygen, sulphur, or nitrogen atom, respectively.

With formaldehyde the spectra are also shifted towards the visible by alkyl substitution, but are moved in the opposite direction by chlorine substitution (*i.e.*, in carbonyl chloride) (Henri; quoted by Mulliken, *J. Physical Chem.*, 1935, **3**, 572). Here the excited electron is in a non-bonding oxygen orbital, and is, therefore, separated by a carbon atom from the chlorine atom. The negative nature of chlorine with respect to carbon decreases the negative charge on the oxygen atom, and the spectrum moves to higher frequencies. In the case of substitution of hydrogen by chlorine in chloroamine, however (where, incidentally, the >N–Cl bond is practically non-polar (Pauling, *J. Amer. Chem. Soc.*, 1932, **54**, 3582)), the excited electron is probably in a bonding orbital, which is in closer proximity to the readily polarisable chlorine atom. Here, as we have observed, the spectrum moves considerably towards the visible.

The author's thanks are due to Prof. F. G. Soper for suggesting the subject and for his continued interest and helpful advice; and to the University of Otago for the award of the George Young and the Duffus Lubecki Scholarship.

UNIVERSITY OF OTAGO, DUNEDIN, N.Z. [*Received, December 1st*, 1941.]

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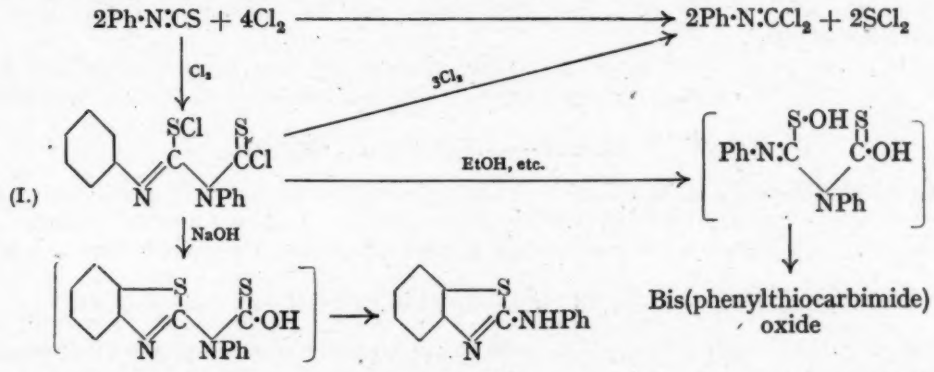
25. *The Action of Chlorine on Aryl Thiocarbimides and the Reactions of Aryl* iso*Cyanodichlorides. Part II.*

By G. MALCOLM DYSON and THOMAS HARRINGTON.

The action of chlorine on thiocarbimides has been further investigated, and a simpler explanation of the observed reactions proposed. From the reaction product of secondary amines and *iso*cyanodichlorides, pentasubstituted guanidines have been isolated. The action of ethyl alcohol on *iso*cyanodichlorides has been shown to be complex, although the corresponding urethane is always a

product of the reaction. Phenols and *iso*cyanodichlorides yield crystalline imido-carbonates. When *iso*cyanodichlorides and a hydrocarbon react in the presence of aluminium chloride, only one chlorine atom is attacked, but when the product is poured into water, further reaction takes place, yielding compounds of the type R·NH·COR'.

DYSON and HARRINGTON (J., 1940, 191) showed that phenylthiocarbimide in an inert solvent is converted by chlorine first into an unstable chloro-addition compound, which yields, on further addition of chlorine, phenyl *iso*cyanodichloride. This chloro-addition compound reacts with alcohol or glacial acetic to form bis(phenylthiocarbimide) oxide and with sodium hydroxide solution, yielding 1-anilinobenzthiazole. A scheme to correlate these reactions was proposed which assumed the existence of two different chloro-addition compounds. It is now considered that these are one and the same, since both react with sodium hydroxide to yield 1-anilinobenzthiazole. The modified scheme is as follows :



The structure of bis(phenylthiocarbimide) oxide can be derived from the reactions (1) oxide + hydrogen ⟶ *s*-diphenylthiourea; (2) oxide + aniline ⟶ *s*-diphenylurea; (3) chloro-addition compound + sodium hydroxide ⟶ 1-anilinobenzthiazole. Reactions (1) and (2) indicate the presence in the oxide of the groups ·S·C(NPh)$_2$ and Ph·N·C·O respectively and reaction (3) indicates the presence of the group ·S·C(:NPh)·NPh in the chloro-addition compound. Since this is so readily converted into the oxide, we can assume that this group is also present in the oxide. Two structures for the oxide are therefore possible :

It has not been possible to discriminate between these two.

The most likely structure of the chloro-addition compound is given by (I), established by empirical analysis only, because of its extreme instability.

Evidence has been obtained to show that during the addition of chlorine to phenylthiocarbimide, chlorination also takes place in the nucleus, yielding *p*-chlorophenyl *iso*cyanodichloride (cf. Nef, *Annalen*, 1892, **270**, 282; Bly, Perkins, and Lewis, *J. Amer. Chem. Soc.*, 1922, **44**, 2896).

The Action of Secondary and Tertiary Amines on iso*Cyanodichlorides.*—Diphenylamine and phenyl *iso*cyanodichloride reacted readily when refluxed in tetrachloroethane solution, yielding *pentaphenylguanidine hydrochloride* almost quantitatively :

$$Ph\cdot N{:}CCl_2 + 2NHPh_2 \longrightarrow Ph\cdot N{:}C(NPh_2)_2,HCl + HCl$$

From other secondary amines and *iso*cyanodichlorides a large amount of tar was produced during the reaction and it was not possible to isolate the guanidine hydrochloride, although in several cases the guanidine itself was obtained.

Tertiary amines and *iso*cyanodichlorides did not react under the usual conditions.

The Action of Alcohols on iso*Cyanodichlorides.*—Sell and Zierold (*Ber.*, 1874, **7**, 1228) reported that phenylurethane was the main product of the reaction between phenyl *iso*cyanodichloride and ethyl alcohol. Lachman (*Ber.*, 1879, **12**, 1349) obtained a mixture of *N*-*o*-tolylurethane and *s*-di-*o*-tolylurea by the reaction of *o*-tolyl *iso*cyanodichloride with alcoholic potassium hydroxide, but the urethane alone by its reaction with sodium ethoxide. Lengfeld and Stieglitz (*J. Amer. Chem. Soc.*, 1894, **16**, 70) and

Smith (*ibid.*, p. 372) obtained ethyl phenylimidochloroformate by treating an ethereal solution of phenyl *iso*cyanodichloride and alcohol at 0° with an ice-cold solution of sodium ethoxide in alcohol. By allowing the reaction to take place at 50°, Smith (*loc. cit.*) obtained ethyl phenylimidocarbonate.

The investigations of Sell and Zierold have been further extended. Both *p*-nitrophenyl and *p*-tolyl *iso*cyanodichloride and ethyl alcohol yielded the corresponding urethane alone, whereas phenyl and *m*-nitrophenyl *iso*cyanodichlorides yielded the urethane and amine hydrochloride; thus phenyl *iso*cyanodichloride produced phenylurethane and aniline hydrochloride. *m*-Tolyl *iso*cyanodichloride and ethyl alcohol produced a mixture of *m*-tolylurethane and the *hydrochloride* of a base whose analysis agreed with the empirical formula $C_{20}H_{22}O_2N_2$,HCl. In the case of *o*-tolyl *iso*cyanodichloride the greater part formed *o*-tolylurethane, but in addition a crystalline substance containing nitrogen and chlorine was isolated: its identity was not determined.

Phenols and iso*Cyanodichlorides.*—Hantzsch and Mai (*Ber.*, 1895, **28**, 977), investigating the reaction between phenyl *iso*cyanodichloride and sodium phenoxides, could not prepare stereoisomeric compounds of the type Ph·N:C(OR)·OR'.

The reaction between *iso*cyanodichlorides and phenols has now been studied. Reaction proceeded vigorously at 150° with evolution of hydrogen chloride and the formation of crystalline trisubstituted imido-carbonates:

$$R\cdot N{:}CCl_2 + 2R'\cdot OH \longrightarrow R\cdot N{:}C(OR')_2 + 2HCl$$

The Friedel–Crafts Reaction applied to iso*Cyanodichlorides.*—When phenyl *iso*cyanodichloride, benzene, and aluminium chloride were refluxed together, reaction took place with evolution of hydrogen chloride, and benzanilide was isolated when the product was poured into water, the reaction being probably as follows:

$$Ph\cdot N{:}CCl_2 + HPh \longrightarrow Ph\cdot N{:}CPhCl \longrightarrow Ph\cdot N{:}CPh\cdot OH \longrightarrow Ph\cdot NH\cdot COPh$$

Attempts to prepare the compound Ph·N:CPh·OEt by pouring the reaction product into ethyl alcohol were not successful.

Experimental.

p-*Chlorophenyl* iso*Cyanodichloride.*—Phenylthiocarbimide (318 g.) in phenyl *iso*cyanodichloride (289 g.) was treated with chlorine (cf. Dyson and Harrington, *loc. cit.*). On fractional distillation, phenyl *iso*cyanodichloride was obtained, followed by a colourless oil (5 g.), b. p. 212—220°, a pale yellow oil (25 g.), b. p. 220—226°, and a pale yellow oil (5 g.), b. p. 226—230°. The product of b. p. 220—226° (10 g.) in benzene was refluxed with aniline (20 g.) for 5 hours, and the precipitated solid collected, digested with concentrated hydrochloric acid, filtered off, and dissolved in boiling water (1 l.). On cooling, triphenylguanidine hydrochloride (2 g.) crystallised; the filtrate, concentrated to 250 ml. and cooled, deposited s-*diphenyl*-p-*chlorophenylguanidine hydrochloride* (10 g.), m. p. 256° (Found: HCl, 10·4. $C_{19}H_{16}N_3Cl$,HCl requires HCl, 10·2%). The corresponding guanidine formed colourless needles, m. p. 136°, from alcohol.

The liquid, b. p. 220—226°, was therefore largely *p*-chlorophenyl *iso*cyanodichloride.

Pentaphenylguanidine Hydrochloride.—Phenyl *iso*cyanodichloride (10 g.) and diphenylamine (20 g.) in tetrachloroethane (25 ml.) were refluxed for 4 hours, much hydrogen chloride being evolved and the liquid becoming dark green. The solid that crystallised on cooling was collected, washed with tetrachloroethane, and recrystallised from alcohol, forming white needles (22 g.), m. p. 227° (Found: HCl, 7·5. $C_{31}H_{25}N_3$,HCl requires HCl, 7·7%).

Pentaphenylguanidine, obtained by neutralisation of a solution of the above, separated from alcohol in white needles, m. p. 179° (cf. Steindorff, *Ber.*, 1904, **37**, 965).

s-*Tetraphenyl*-p-*tolylguanidine.*—*p*-Tolyl *iso*cyanodichloride (5 g.) and diphenylamine (9 g.) in tetrachloroethane (20 ml.) were refluxed for 3 hours. As a solid was not deposited on cooling, the solvent was removed on an oil-bath, and the residual tar extracted with boiling water. The hot extract was treated with 2N-sodium hydroxide, and the precipitated *base* collected and crystallised from alcohol; it formed small yellow needles (6 g.), m. p. 175° (Found: N, 9·3. $C_{32}H_{27}N_3$ requires N, 9·3%).

s-*Tetraphenyl*-m-*tolylguanidine*, yellow needles, m. p. 174—176° (Found: N, 9·2%), and s-*tetraphenyl*-o-*tolylguanidine*, yellow needles, m. p. 172° (Found: N, 9·2%), were also prepared.

p-*Tolylurethane.*—*p*-Tolyl *iso*cyanodichloride (20 g.) was dissolved in alcohol (50 ml.) and gradually warmed on the water-bath. When the vigorous reaction had subsided, refluxing was continued for a further ½ hour; on cooling, p-*tolylurethane* crystallised in white needles, m. p. 51° (Found: N, 7·7. $C_{10}H_{13}O_2N$ requires N, 7·8%). p-*Nitrophenylurethane*, m. p. 127°, white needles, was obtained in a similar way (Found: N, 13·2. $C_9H_{10}O_4N_2$ requires N, 13·3%). The yields in both cases were almost theoretical.

Phenyl iso*Cyanodichloride and Ethyl Alcohol.*—Phenyl *iso*cyanodichloride (20 g.) was treated with alcohol (50 ml.) as above, and the alcohol removed on the water-bath. On cooling, the oil which remained solidified and consisted of a mixture of phenylurethane and aniline hydrochloride. The urethane was extracted with

ligroin and after concentration, crystallised in colourless needles, m. p. and mixed m. p. 54°. The aniline hydrochloride was crystallised from aqueous alcohol; m. p. 198° In the same way *m*-nitrophenyl *iso*cyanodichloride yielded *m*-nitrophenylurethane, pale yellow needles from alcohol, m. p. 56°, and *m*-nitroaniline hydrochloride, m. p. 230°.

m-*Tolyl* iso*Cyanodichloride and Ethyl Alcohol.*—*m*-Tolyl *iso*cyanodichloride (20 g.) and ethyl alcohol (50 ml.) were refluxed for ½ hour on the water-bath, the alcohol was distilled off, and the oily solid shaken with water. The oil which separated was extracted with ether, the extract dried with calcium chloride, and the ether distilled. The remaining oil distilled as *m*-tolylurethane (6 g.), a colourless liquid, b. p. 250—255° (decomp.).

Sodium hydroxide solution was added to the aqueous portion above; the precipitated base was collected and crystallised from alcohol, forming colourless needles (7 g.), m. p. 82°. The base was dissolved in warm alcohol, just acidified with concentrated hydrochloric acid, and cooled; the *hydrochloride* crystallised in colourless plates, m. p. 270° (Found: HCl, 10·4; N, 8·0. $C_{20}H_{22}O_2N_2$,HCl requires HCl, 10·2; N, 7·8%).

o-*Tolyl* iso*Cyanodichloride and Ethyl Alcohol.*—*o*-Tolyl *iso*cyanodichloride (20 g.) and ethyl alcohol (50 ml.) were treated as above. The excess of alcohol was driven off on the water-bath, and the residue steam-distilled, giving approximately equal weights of materials having m. p. 34°, 36°, 65°, 100°, and 105°. The first and second, crystallised from alcohol, gave *o*-tolylurethane (6 g.), m. p. 45°. The fourth and fifth portions crystallised from ligroin in long, feathery, white needles, m. p. 108°, containing nitrogen and chlorine (Found: *M*, 182).

Phenyl Phenylimidocarbonate.—Phenyl *iso*cyanodichloride (10 g.) and phenol (10 g.) were heated for an hour at 150°. Vigorous evolution of hydrogen chloride occurred. The product was a clear golden-yellow liquid which on cooling set to a hard glass. This was crystallised from benzene (25 ml.), giving short white prisms (10 g.), m. p. 130°, and recrystallised from alcohol, forming needles, m. p. 136° (Found: N, 4·8. $C_{19}H_{15}O_2N$ requires N, 4·8%).

p-*Tolyl phenylimidocarbonate*, colourless needles, m. p. 110° (Found: N, 4·3. $C_{21}H_{19}O_2N$ requires N, 4·4%), *phenyl* p-*tolylimidocarbonate*, needles, m. p. 108° (Found: N, 4·4. $C_{20}H_{17}O_2N$ requires N, 4·6%), p-*tolyl* o-*tolylimidocarbonate*, long colourless needles, m. p. 115° (Found: N, 4·2. $C_{22}H_{21}O_2N$ requires N, 4·2%), *phenyl* p-*bromophenylimidocarbonate*, plates, m. p. 154° (Found: N, 3·7. $C_{19}H_{14}O_2NBr$ requires N, 3·8%), *phenyl* p-*nitrophenylimidocarbonate*, pale yellow needles, m. p. 165° (Found: N, 8·0. $C_{19}H_{14}O_4N_2$ requires N, 8·4%), and p-*chlorophenyl* p-*nitrophenylimidocarbonate*, pale yellow needles, m. p. 185° (Found: N, 6·6. $C_{19}H_{12}O_4N_2Cl_2$ requires N, 6·9%), were also prepared.

Benzanilide.—Aluminium chloride (35 g.) reacted slowly with phenyl *iso*cyanodichloride (20 g.) in cold benzene (50 ml.), but on the water-bath hydrogen chloride was profusely evolved. After ½ hour's heating, the mixture was poured into cold water (500 ml.). The crystals (22 g.) that formed in the benzene layer were identified as benzanilide, m. p. 162° (Found: N, 7·1. Calc.: N, 7·1%).

Benzo-*p*-toluidide, m. p. 158°, and benzo-*o*-toluidide, m. p. 143°, were also prepared.

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26. *Comments on the Mechanisms of Covalent-bond Fission.*

By WILLIAM A. WATERS.

It is pointed out that there is a close connection between the electrostatic dipole energy and the resonance energy of any unsymmetrical covalent bond. The electrostatic factors determining the activation energies of both ionic and neutral reactions are compared, and it is shown that the favoured mechanism for unimolecular dissociation is largely determined by the dielectric constant of the solvent medium.

1. *Electrostatic Energy and Resonance Energy.*—In dealing with polar reactions (J., 1933, 1551) the author pointed out that the electrostatic energy, $E_c = \frac{1}{2}\mu^2/\alpha$, which can be associated with any unsymmetrical covalent bond, of dipole moment μ and polarisability α, plays a significant part in predisposing polar molecules to act in particular ways. Moreover, it was shown that internal inductive effects in complex molecules produced great changes in this electrostatic bond energy. Today, theories of "induced polarity" have been so overshadowed by the more general conception of "resonance" that it is of value to compare, for bonds between unlike atoms, A–B, this electrostatic energy E_c—which is the Coulombic energy associated with the unsymmetrical mean positions of the valency electrons—with the total "ionic resonance energy", E_R, defined by Pauling ("The Nature of the Chemical Bond," Chap. II, Cornell Univ. Press, 1940) as the difference between the total energy of the bond A–B and the mean of the bond energies of the links A–A and B–B, *i.e.*,

$$E_R = E_{(A-B)} - \tfrac{1}{2}\{E_{(A-A)} + E_{(B-B)}\}$$

TABLE I.

Electrostatic Energies and Resonance Energies of Covalent Bonds.

N_D = Bond refractivity (cf. Fajans and Knorr, *Ber.*, 1926, **59**, 249).
a = Bond polarisability.
μ = Bond dipole moment (taken from Pauling, *op. cit.*).
E_e = Electrostatic bond energy = $\frac{1}{2}\mu^2/a$.
E_R = Ionic resonance energy (Pauling, *op. cit.*, p. 59)

Bond.	N_D.	$a \times 10^{24}$ (c.c.).	$\mu \times 10^{18}$ (e.s.u.).	E_e (kg.-cals.).	E_R (kg.-cals.).	Bond.	N_D.	$a \times 10^{24}$ (c.c.).	$\mu \times 10^{18}$ (e.s.u.).	E_e (kg.-cals.).	E_R (kg.-cals.).
H–F	1·90	0·749	(2)	38·5	64·0	C–F	1·60	0·630	1·4	22·5	45·9
H–O	1·88	0·741	1·51	22·3	41·0	C–O	1·46	0·575	0·8	6·40	23·2
H–N	1·87	0·737	1·31	16·8	22·0	C–N	1·45	0·571	0·4	2·03	9·3
H–C	1·70	0·669	0·4	1·73	6·3	C–C	1·21	0·476	0·0	0·0	0·0
H–S	4·77	1·88	0·68	1·78	3·9	N–N	1·46	0·575	0·0	0·0	0·0
H–Cl	6·67	2·62	1·03	2·93	22·1	N–O	1·72	0·676	0·5?	2·13	—
H–Br	9·17	3·61	0·78	1·22	12·5	O–O	2·22	0·874	0·0	0·0	0·0
H–I	13·74	5·41	0·38	0·19	1·6	S–S	8·15	3·21	0·0	0·0	0·0
						Cl–Cl	11·64	4·59	0·0	0·0	0·0
$\overset{+}{N}$–N	1·4	0·55	2·0?	5·24	—	C–S	4·67	1·84	1·2	5·68	6·7
C=O	3·42	1·34	2·8	42·3	54·0*	C–Cl	6·57	2·59	1·5	6·28	8·3
C=S	12·5	4·92	3·0	13·2	15·0*	C–Br	9·47	3·73	1·4	3·80	1·6
C=N	4·93	1·95	—	—	—	C–I	14·51	5·72	1·2	1·82	−1·9
N=O	4·80	1·89	1·9	13·8	—	N–Cl	6·91	2·72	0·0?	—	−0·5

The bond refractivities calculated for compounds of nitrogen, oxygen, etc., include aliquot portions of the refractivity due to any unshared electron pairs. This is justifiable, for one can presume that the electronic atmosphere surrounding any atomic nucleus would tend to move as a whole in any applied electric field. Refractivities for sulphur compounds have been calculated from atomic refractivities given by Price and Twiss (J., 1912, **101**, 1259). Resonance energies marked * have been computed from Sidgwick's thermal data (" The Nature of the Covalent Link," 1931). The partly ionised link N^+—N is that of hydrazine salts: its dipole moment is computed on the assumption that one atom has an effective nuclear charge, after allowing for electron screening, of 0·6 unit (Pauling, *op. cit.*, p. 65).

Of the data in the above table, those for the bond refractivities are most open to doubt, but it will be seen that values for series of links, such as C–F, C–O, C–N, C–C, lie on smooth curves, such as one would draw for purposes of interpolation.

It will be seen from Table I that the Coulombic energy, E_e, of a bond is usually the major portion of the ionic resonance energy, and often gives a better criterion of the extent of internal resonance in a polar bond than does the dipole moment alone. One can ascribe the non-Coulombic fraction of the bond resonance energy to the contraction effect in resonance systems.

2. *Energy Requirements for Unimolecular Dissociations.*—It is a fundamental postulate of the theory of resonance that the larger the ionic resonance energy, E_R, of an unsymmetrical bond, A–B, the greater is the extent to which the ionic state $A^+ B^-$ participates in its bond structure. Consequently, the probability that bond-fission processes will take the unsymmetrical course, A–B $\longrightarrow$ $A^+ + B^-$, to yield two ions, and not the symmetrical course, A–B $\longrightarrow$ $A^\cdot + {}^\cdot B$, to yield two neutral radicals, becomes greater as this energy increases. Pauling ascribes 50% of ionic character to an unsymmetrical covalent bond having an ionic resonance energy of about 50 kg.-cals., and for such a bond, *ceteris paribus*, the ionic and the free-radical dissociation processes should be equally probable.

To complete an ionic dissociation, however, one must separate the mutually attracting ions resulting from the bond fission. This requires an amount of energy which depends very much upon the environment of the reactant molecule, and one can instance many molecules (*e.g.*, CH_3I, ICl, SO_2Cl_2) which, when in solution, can undergo reactions of both types according to the nature of the chemical change involved.

Table II shows that the electrostatic energy needed to create a single gaseous ion, $E_i = \frac{1}{2}N\varepsilon^2/r$, is greater than the thermal energy needed to dissociate a covalent bond into *two* neutral radicals, but shows, too, how great can be the dielectric effect of a solvent in reducing the electrostatic energy of ion formation. At interatomic distances the effective value of D is not that of the solvent in bulk, but is very much less (compare Waters, *Trans. Faraday Soc.*, 1938, **34**, 115), and one cannot say that an ion is " free " (*i.e.*, completely dissociated) until it is separated from every other one by a sheath of solvent several molecules thick. Consequently, expressions containing the measurable dielectric constant of the solvent can only be used in computing the energy of the final stage of a dissociation process. Completed changes only are considered in this section of the paper. In transition states D is a function of interatomic distance, but when this is the case the total energy of any ion or radical includes both Coulombic and interchange energy terms.

TABLE II.

Electrostatic Energies of Some Common Ions.

Ion.	Ionic radius, A.	$E_i = \frac{1}{2}Ne^2/Dr$, kg.-cals. ($D = 1$).	($D = 80$).	Ion.	Ionic radius, A.	$E_i = \frac{1}{2}Ne^2/Dr$, kg.-cals. ($D = 1$).	($D = 80$).
F^-	1·36	121·0	1·5	$Alkyl^+$ (CH_3^+)	2·0	82·4	1·0
Cl^-	1·80	91·5	1·2	H^+ (solvated)	1·2	137·3	1·7
Br^-	1·95	84·5	1·1	N^+ (ammonium salts) ...	1·5	110·0	1·4
I^-	2·15	76·6	1·0	SH^- (RS^-)	1·85	89·0	1·1
OH^- ($R{-}O^-$)	1·40	118·0	1·5				

The ionic radii used above are the van der Waals radii (Pauling, *op. cit.*, p. 189), which give the minimum distances of approach of charged particles capable of independent motion. These distances are very much bigger than the covalent radii of the same groups, and this enlargement of the radius of domain of an ion is an essential feature of unsymmetrical covalent-bond fission. For anions, this enlargement is due to an expansion of the outer electronic shell following the reduction of the restraining positive charge, and for the non-metallic kations the expansion is due to complex formation with solvent molecules, since there is no corresponding expansion on the ionisation of metals.

The electrostatic energy of solvation of kations, such as H^+ or $Alkyl^+$, which are stabilised by co-ordinate-link formation with solvent molecules, is very much greater than the possible thermal energy of co-ordination processes, such as $H^+ \leftarrow OH_2$, which give to each component atom completed electron shells. Calculations on the lines of Table II, using covalent radii instead of van der Waals radii, indicate that bare kations would possess exceptionally large electrostatic energies, and it is attractive to equate the electrostatic energy lost by group expansion to the hypothetical heat of formation of the solvate links. The expansion of the hydrogen atom (radius 0·3 A.) in water on formation of the hydrated ion H_3O^+ (radius 1·2 A.) is such as to correspond to a reduction of its ionic energy in this solvent by 6·8 kg.-cals., a value quite reasonable for the process H^+ (dissolved) + $OH_2 = (H \leftarrow OH_2)^+$.

The energy changes occurring when ions are transferred from one environment to another are so preponderatingly large that one can deduce, by the following argument, that the dielectric constant of the solvent medium is the dominant physical factor in determining the mode of bond fission. When an unsymmetrical covalent bond, $\overset{+}{A}\!\!\rightarrow\!\!\overset{-}{B}$, dissociates into two neutral radicals, work = E_c (see above) must be done, whatever the dielectric constant of the solvent, to overcome the electrostatic energy of the dipole, in addition to work = E_q which must be done against non-Coulombic quantum forces. In contrast, if the bond dissociates into the *completely separated* ions A^+ and B^-, then electrostatic energy = ($\Sigma E_{ions} - E_c$) must be supplied, in addition to energy, $E_{q'}$, needed to overcome quantum forces. Unless E_q and $E_{q'}$ are *very* greatly different in magnitude, which seems unlikely,* it follows that a critical condition for preferential neutral radical or ionic dissociation is reached when $E_{ions} \simeq 2E_c$, *i.e.*, when $\frac{1}{2}\epsilon^2(1/r_A + 1/r_B)/D \simeq \mu^2\alpha$.

The foregoing treatment of the ionisation of a covalent bond makes the assumption that a covalent bond gradually expands before fission, and that the electron-switch from the covalent to the ionised structure is not fully effected until each component ion has expanded to the dimensions which it would have in the free state. If, however, one considers that the transition of a covalent bond to an ion-pair state can be effected instantly, then the electrostatic energy of the ion-pair, ϵ^2/Dd, where d is the length of the covalent bond, must be used in place of ΣE_{ions}. Table III shows that substantially the same conclusions are reached by the use of either formula.

The electrostatic energies, E_c of Table III are those for substituent groups attached to normal paraffin chains. Reference to the author's electrostatic treatment of induced polarity (*loc. cit.*) will show how

* It is difficult to find much experimental data to test this, but the following figures, taken from Pauling (*op. cit.*, pp. 23, 66) and from Table II, show that the total excess energy of ions A^+ and A^- over radicals, $2A\cdot$, is nearly all Coulombic.

Atom.	Total energy of reaction $A^+ + A^- = A\cdot + \cdot A$, kg.-cals.	$2 \times E_{ion}$ (Table II), kg.-cals.
Hydrogen	312·0 − 16·4 = 295·6	274·6
Fluorine	429·0 − 98·5 = 230·5	242·0
Chlorine	298·9 − 92·5 = 206·4	183·0
Bromine	272·1 − 87·1 = 185·0	169·0
Iodine	240·8 − 79·2 = 161·6	153·2

Energy differences of 20 kg.-cals. (well within figures computed from estimated ionic radii) are too small to affect the purport of the main argument of this paper.

Further theoretical support for the hypothesis that $E_q \simeq E_{q'}$ may be drawn from Section I, where it is pointed out that a large part of the ionic resonance energy of unsymmetrical covalent bond formation is electrostatic energy, E_c.

TABLE III.

Effect of the Dielectric Constant upon the Energy of Ion Formation.

E_c = Electrostatic bond energy, $\frac{1}{2}\mu^2/a$.
d = Normal bond length.
$E_{\text{ion-pair}} = N\epsilon^2/Dd$.
$\Sigma E_{\text{ions}} = \frac{1}{2}N\epsilon^2(1/r_A + 1/r_B)/D$.

Bond.	d, A.	E_c, kg.-cals.	$E_{\text{ion-pair}}$ ($D = 1$), kg.-cals.	ΣE_{ions} ($D = 1$), kg.-cals.	Critical values for D. For ion-pair.	Critical values for D. For free ions.
C–F	1·41	22·5	233·5	203·3	4·6	5·2
C–Cl	1·76	6·26	187·1	173·8	15	14
C–Br	1·88	3·80	175·2	167·0	23	22
C–I	2·05	1·82	160·6	158·0	44	44
C–OH (C–OR)	1·43	6·4	230·3	200·0	18	16
C–N	1·47	2·03	224·0	192·0	55	47
N^+–N	1·38	5·24	238·6	219·0	23	21
O–H	0·97	22·3	339·1	255·3	7·6	5·7
N–H	1·01	16·8	326·1	247·1	9·7	7·3
S–H	1·35	5·68	244·0	226·3	22	20
C–H	1·09	1·73	302·2	220·0	113	64

easily one might, by varying a distant substituent group in a covalent molecule, bring about a complete change in the mechanism of a dissociation reaction. Induction effects, and also electrical dipole–solvent interactions (cf. Sutton, *Ann. Reports*, 1940) which reduce the magnitude of E_c should tend to assist neutral radical formation and *vice versa*. Calculations on the above lines show that the attainment of a complete reversal of mode of polar fission, which has formerly been suggested for reactions of "positive halogen compounds" (*i.e.*, reactions of oxidising type depictable as proceeding by the fission R—Cl $\longrightarrow$ R^- + Cl^+, as in the *N*-chloroamines), is most improbable, and substantiate the view that these molecules react by dissociating into neutral radicals (compare Waters, J., 1937, 2010).

The dielectric constants of common solvents of organic chemistry are listed below (Table IV). It will be seen that the direct dissociation of the hydrogen–carbon link should, in nearly all solvents, give neutral radicals, but that covalent bonds linking hydrogen to oxygen, sulphur, or nitrogen should break to yield hydrogen kations. Carbon–halogen bonds should dissociate to give neutral radicals in solvents with $D<5$ and to give ions in solvents with $D>20$. Only in a very few solvents do the two dissociation processes require comparable energy increments. These broad conclusions are in full accord with experimental facts.

TABLE IV.

Dielectric Constants of Common Solvents.

*cyclo*Hexane	2·0	Favour neutral radicals
Carbon tetrachloride	2·2	
Benzene	2·3	
Carbon disulphide	2·6	
Ether	4·3	
Chloroform	4·7	
Ethyl acetate	6·4	
Acetic acid	7·1	
Pyridine	12·5	Usually favour ions
Sulphur dioxide	15·6	
Acetone	19·6	
Liquid ammonia	22·0	
Ethyl alcohol	25·0	
Methyl alcohol	32·4	
Nitrobenzene	36·0	
Formic acid	48·0	
Water	80·0	Ionisation exclusively
Hydrogen cyanide	95·0	

3. *Bimolecular Reactions.*—The activation energy of a bimolecular reaction is the difference in energy between the initial state, A + B–C, and the critical complex A · · · B · · · C in which the covalent bond B–C has not been severed completely. The activation energy of an ionic interchange, such as HO^- + CH_3–I $\longrightarrow$ HO–CH_3 + I^-, is affected by the dielectric constant of the solvent in just the same way as is a simple unimolecular ionisation, since one of the initial reactants is an ion whilst the critical complex is a tripole having a net resultant charge.

For the simplified case where A and C are the same [*e.g.*, for an exchange reaction of the type of $(Br^*)^-$ + Bu–Br $\longrightarrow$ Br^*–Bu + Br^-] the overall electrostatic energy change of the bimolecular reaction is

$$3\epsilon^2/2Dd - (\epsilon^2/2Dr_A + E_c)$$

where d is the distance between the ionic centres A · · · B in the tripole complex. For the corresponding unimolecular dissociation of B–A the electrostatic energy required is $(\varepsilon^2/Dd - E_c)$.

If one assumes that d is nearly the same in both cases, then more electrostatic energy is required to bring about a bimolecular than a unimolecular reaction if $\varepsilon^2/2Dd > \varepsilon^2/2Dr_A$ or, more simply, if $r_A > d$, provided one compares transition states for which D is the same.

Inspection of Tables II and III shows that r_A and d are almost of equal magnitude for alkyl halides, and hence one can understand why the activation energies of their unimolecular and bimolecular reactions are comparable.

In conclusion, it may be pointed out that both for the unimolecular and for the bimolecular ionic reactions the total activation energy $E = E_{q'} + E_{\text{electrostatic}}$ is a function of the type $E = E_1 + E_2/D$, as suggested on both theoretical and experimental grounds for equilibria by Wynne-Jones (*Proc. Roy. Soc.*, 1933, *A*, **140**, 443) and for reactions by Evans and Jenkins (*Trans. Faraday Soc.*, 1940, **36**, 818).

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27. *The Interaction of Chloramine-T and Hydrogen Sulphide, Phosphine, and Arsine.*

By JAMES R. BENDALL, FREDERICK G. MANN, and DONALD PURDIE.

Hydrogen sulphide and sodium sulphide react with aqueous chloramine-T to give sulphuric acid and sulphur respectively. Sulphites are quantitatively oxidised to sulphates and can be thus estimated volumetrically, whereas thiosulphates are converted into tetrathionates.

Chloramine-T, reacting with an excess of phosphine, oxidises it to hypophosphorous and phosphorous acids. When the chloramine-T is in excess, complete but slow oxidation to phosphoric acid occurs, the slow intermediate stage being the oxidation of the hypophosphorous to phosphorous acid.

Chloramine-T oxidises arsine rapidly to arsenic acid, irrespective of the proportions of the reactants; the initial oxidation to arsenious acid is, however, slower than the oxidation of the latter to arsenic acid.

A STUDY of the interaction of chloramine-T (p-$C_6H_4Me{\cdot}SO_2{\cdot}NNaCl,3H_2O$) with hydrogen sulphide, phosphine, and arsine has revealed several points of interest that warrant detailed quantitative investigation, but present circumstances have allowed only the recognition of the main reactions involved.

The interaction of chloramine-T and the chief organic derivatives of 2-covalent sulphur is now well established: organic sulphides of type R_2S give "sulphilimines" * (I), a reaction also shown by some cyclic sulphides (Mann and Pope, J., 1922, **121**, 1052); thiols give compounds of type (II) (Clarke, Kenyon, and Phillips, J., 1930, 1225); disulphides, R_2S_2, with an excess of the reagent undergo fission at the

(I.) $R_2S{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$ $\qquad$ $RS{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$ (II.)
$\qquad\qquad\qquad\qquad\qquad\qquad\quad NH{\cdot}SO_2{\cdot}C_6H_4Me$

S–S linkage, each fragment then furnishing a molecule of type (II) (Alexander and McCombie, J., 1932, 2087). The interaction of chloramine-T with hydrogen sulphide has therefore been investigated, since this reaction might produce the parent unsubstituted sulphilimine, $H_2S{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$, which furthermore by hydrolysis might furnish the unknown dihydrogen sulphoxide, $H_2S{\rightarrow}O$, probably tautomeric with the compound H·S·OH.

When, however, an excess of hydrogen sulphide was passed into an aqueous solution of chloramine-T at room temperature, p-toluenesulphonamide was precipitated and sulphuric acid formed; no sulphurous acid, and only a trace of sulphur, could be detected, and the reaction evidently follows equation (A).

$$H_2S + 4C_6H_4Me{\cdot}SO_2{\cdot}NNaCl + 4H_2O = H_2SO_4 + 4C_6H_4Me{\cdot}SO_2{\cdot}NH_2 + 4NaCl \quad . \; . \; . \; . \; . \; (A)$$

This is confirmed by the almost theoretical yields of the amide and of sulphuric acid, calculated on the chloramine-T used. No indication of sulphilimine formation could be obtained. It follows from these

* Mann and Pope gave the name "sulphilimine" to this class of compound on the advice of the late Mr. A. J. Greenaway, who named a specific member, *e.g.*, $Et_2S{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$, "diethylsulphine-$p$-toluenesulphonylimine." It is clear that on the latter basis the term for this class of compound should be "sulphinimine," a name which moreover would accord with the similar "phosphinimine" and "arsinimine." The phosphinimines are represented by two types (*a*) $R_3P{\rightarrow}NR$ (Staudinger and Hauser, *Helv. Chim. Acta*, 1921, **4**, 861) and (*b*) $R_3P{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$ (Mann and Chaplin, J., 1937, 527), and the arsinimines by $R_3As{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$ (Mann, J., 1932, 958; Mann and Chaplin, *loc. cit.*).

results that the further oxidation of any intermediate oxy-acids of sulphur (*e.g.*, H_2SO) formed in the course of this reaction must be very rapid compared with initial oxidation of the hydrogen sulphide, and the possibility of their isolation must be remote.

When a standard sodium sulphide solution was titrated with chloramine-T, with potassium iodide–starch as an external indicator, sulphur was deposited and the solution became markedly alkaline, no trace of sulphite or sulphate being detected; although the end-point was far from sharp, the results indicated clearly that the main reaction followed equation (B). [Alternatively, since sodium sulphide

$$\bar{\bar{S}} + C_6H_4Me{\cdot}SO_2{\cdot}NNaCl + 2H_2O = S + C_6H_4Me{\cdot}SO_2{\cdot}NH_2 + NaCl + 2\bar{O}H \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

is largely hydrolysed at the dilution employed, this reaction may have followed equation (B1), the two

$$\bar{S}H + \bar{O}H + C_6H_4Me{\cdot}SO_2{\cdot}NNaCl + H_2O = S + C_6H_4Me{\cdot}SO_2{\cdot}NH_2 + NaCl + 2\bar{O}H \quad . \quad . \quad . \quad (B1)$$

routes being, of course, quantitatively identical.] No further oxidation was caused by the addition of excess of chloramine-T, and therefore even freshly deposited sulphur is not oxidised by this reagent in cold aqueous solution. Sulphur was again deposited when conversely the sodium sulphide solution was added to the chloramine-T. It follows that the oxidation of hydrogen sulphide molecules and of sulphide or hydrosulphide ions is entirely distinct, and that elementary sulphur cannot be an intermediate stage in the oxidation of hydrogen sulphide to sulphuric acid. It is suggested that in the reaction with hydrogen sulphide the trace of sulphur arises from the ionised, and the sulphuric acid from the un-ionised, hydrogen sulphide.

There is a further point of interest concerning the interaction of hydrogen sulphide and chloramine-T. When a standard dilute solution of the latter was titrated with a standard solution of the former, with potassium iodide–starch as *external* indicator, the results showed, as expected, that the reaction again followed equation (A), although the process, owing to experimental error, was useless for accurate analysis. When the order of titration was reversed, the same results were obtained, although the experimental error in the titration—due chiefly to volatilisation of hydrogen sulphide—was now greater. In each case, however, the sulphide was oxidised to sulphuric acid and not to sulphur. If, however, in the second titration the same indicator was used *internally*, the reaction followed an entirely different course, sulphur alone being formed by the oxidation, and considerably less chloramine-T solution being therefore required. This difference in reaction is ascribed to the probability that in the latter reaction oxidation of the potassium iodide by the chloramine-T precedes that of the hydrogen sulphide, the iodine thus formed then oxidising the hydrogen sulphide to sulphur: the ionic oxidation of the iodide would naturally be more rapid than the molecular oxidation of the hydrogen sulphide.

We have also investigated the interaction of chloramine-T with sodium sulphite and sodium thiosulphate. The sulphite in cold aqueous solution is rapidly and quantitatively oxidised to sulphate (equation C), and may be accurately estimated by this method. Sodium thiosulphate is oxidised to

$$Na_2SO_3 + C_6H_4Me{\cdot}SO_2{\cdot}NNaCl + H_2O = Na_2SO_4 + C_6H_4Me{\cdot}SO_2{\cdot}NH_2 + NaCl \quad . \quad . \quad . \quad . \quad . \quad (C)$$

tetrathionate, but the reaction is of little analytical value, as the end-point is not sharp. The main reaction (D) is of interest, however, because again (as in B) the interaction of two neutral substances produces an alkaline solution.

$$2Na_2S_2O_3 + C_6H_4Me{\cdot}SO_2{\cdot}NNaCl + 2H_2O = Na_2S_4O_6 + C_6H_4Me{\cdot}SO_2{\cdot}NH_2 + 2NaOH + NaCl \quad . \quad (D)$$

The complete interaction of phosphine with excess of chloramine-T in aqueous solution at room temperature is much slower than that of hydrogen sulphide. Preliminary experiments showed, however, that when *excess* of phosphine was passed into chloramine-T solution until saturation was obtained and all reaction was complete, the solution contained hypophosphorous and phosphorous acids but no phosphoric acid. Now, the initial reaction of the phosphine was obviously rapid, since if the passage of the gas was stopped before saturation was attained, the odour of the phosphine almost immediately disappeared; the same volume of pure water, similarly treated with phosphine, smelt of the gas for many hours. It follows that the oxidation of hypophosphorous or of phosphorous acid to phosphoric acid (see below) must be a markedly slower process than the rapid initial oxidation of the phosphine to the intermediate acids; had the reverse been the case, only phosphoric acid would have been obtained. (No evidence for the formation of a true phosphinimine, $H_3P{\rightarrow}N{\cdot}SO_2{\cdot}C_6H_4Me$, could be obtained in these experiments.)

The oxidation of phosphine by *excess* of chloramine-T was therefore quantitatively investigated. A limited quantity of phosphine was passed into a considerable excess of aqueous chloramine-T solution

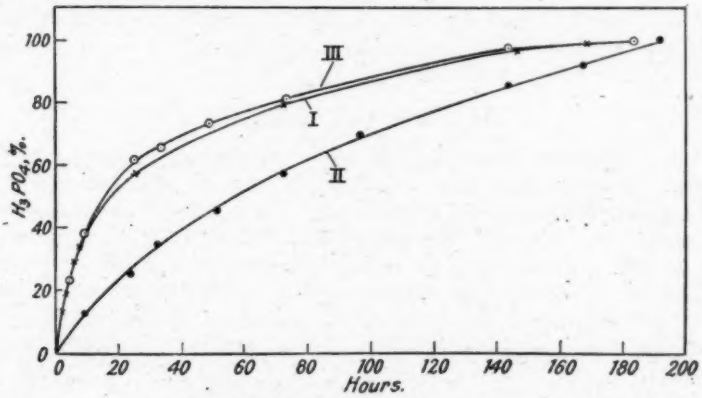
kept at 28·5°. In these circumstances, complete but slow oxidation to phosphoric acid occurred. Aliquot portions of the solution were withdrawn at intervals, and the phosphate content estimated; the total phosphorus content was also determined, so that the percentage of phosphorus present as phosphate at known intervals could be calculated. The results are plotted in curve I, which shows that the production of phosphoric acid is comparatively rapid at first and gradually slackens, and is not complete until the oxidation has proceeded for *ca.* 190 hours.

Now the oxidation of phosphine to phosphoric acid must proceed through the stages A, B, and C, although stage A may actually be a double stage, involving the unknown and presumably very reactive

$$PH_3 \xrightarrow{A} H_3PO_2 \xrightarrow{B} H_3PO_3 \xrightarrow{C} H_3PO_4$$

intermediate $H_3P \rightarrow O$ or $H_2P(OH)$. We consider these stages in reverse order:

Stage C. (*a*) When neutral sodium phosphite (Na_2HPO_3) was treated in aqueous solution with excess of chloramine-T at 28·5°, no appreciable oxidation occurred during 24 hours. (*b*) When, however, the sodium phosphite was treated with 2 equivs. of acetic acid in order to produce an equilibrium with sodium acetate and phosphorous acid, oxidation by chloramine-T was complete in 1 hour, and was too rapid to be followed accurately by timed volumetric analysis. Stage C cannot therefore be responsible for the slow over-all oxidation of the phosphine.



I. *Oxidation of Phosphine.*
II. *Oxidation of* NaH_2PO_2.
III. *Oxidation of* $NaH_2PO_2 + CH_3 \cdot CO_2H$.

Stage B. (*a*) When neutral sodium hypophosphite (NaH_2PO_2) was similarly treated with excess of chloramine-T, a slower but more regular oxidation was obtained (curve II) than with phosphine. Now this oxidation must proceed through the stages B′ and C′, *i.e.*, the first product of oxidation will be

$$NaH_2PO_2 \xrightarrow{B'} NaH_2PO_3 \xrightarrow{C'} NaH_2PO_4$$

weakly *acid* sodium dihydrogen phosphite, which, from the previous results, is almost certainly rapidly oxidised to the phosphate. If therefore stage C′ is very rapid, curve II shows essentially the rate of stage B′. (*b*) When, however, the neutral sodium hypophosphite was first diluted in solution with 1 equiv. of acetic acid, curve III was obtained. This curve, representing stage B, approximated closely throughout its entire length to curve I. It should be emphasised, however, that a strict quantitative comparison between these three curves is not possible, as the amount of phosphine used in (I) could not be accurately predetermined, although it was very small compared with the large excess of chloramine-T used. Repetitions of the phosphine experiment, however, always gave a curve almost identical with I, and lying between curves II and III, and usually—as in the example shown—closely approaching curve III throughout. The general and closely similar character of the three curves is thus not in doubt. In view, therefore, of the rapidity of stages A and C, and the extreme slowness of stage B, it is clear that it is the latter stage, *i.e.*, oxidation of hypophosphorous to phosphorous acid, which is the governing time factor in the over-all oxidation of phosphine to phosphoric acid.

To check these results, the experiments were repeated at 38·5°, a different method being used for phosphate estimation. The curves I, II, and III now obtained were closely similar to the previous ones, except that the initial oxidation in II and III was rather more rapid than at 28·5°, although the time required for almost complete oxidation was virtually unchanged. Disodium hydrogen phosphite

at the higher temperature again underwent no appreciable oxidation in pure aqueous solution, and rapid oxidation in the acetic acid solution.

Comparison of these results with those obtained for the oxidation of the phosphorous acids by halogens is of interest. Manchot and Steinhäuser (*Z. anorg. Chem.*, 1924, **138**, 304) have shown that hypophosphorous acid is oxidised by bromine only slowly in acid solution, but more rapidly in alkaline (*i.e.*, sodium acetate) solution. Various workers (Ruff and Finck, *Arch. Pharm.*, 1902, **240**, 663; Steele, J., 1907, **91**, 1642; Wolf and Jung, *Z. anorg. Chem.*, 1931, **201**, 337) have shown, however, that hypophosphorous acid is oxidised by iodine rapidly in acid solution but negligibly so in alkaline (sodium bicarbonate) solution. Chloramine-T is intermediate between these halogens, since it gives slow oxidation in a solution of sodium hypophosphite originally neutral, but more rapid oxidation in the presence of acetic acid. (The effect of the presence of acids stronger than acetic acid would probably repay investigation.) Comparison of the oxidation of phosphorus acid is difficult, because, although Manchot and Steinhäuser (*loc. cit.*) and Ruff and Finck (*loc. cit.*) state that oxidation of this acid by bromine and iodine is retarded in acid solution but accelerated in alkaline (sodium bicarbonate) solution, Steele (*loc. cit.*) and Mitchell (J., 1923, **123**, 2241) agree that the oxidation by iodine involves two reactions, one retarded and the other accelerated by acids. This acceleration by acids is, of course, the marked feature of the oxidation of sodium phosphite by chloramine-T.

When a current of arsine was passed into a standard solution of chloramine-T until reaction was complete, the solution was found to contain arsenic acid equivalent to the chloramine-T used, and only a trace of arsenious acid was present. (No indication of the formation of an arsinimine was obtained.) It follows that if the oxidation proceeds through the stages

$$AsH_3 \xrightarrow{D} H_3AsO_3 \xrightarrow{E} H_3AsO_4$$

stage E is probably more rapid than stage D. The rapidity of stage E was confirmed by the following experiments. A current of arsine was passed into a solution of chloramine-T at room temperature and stopped whilst there was still a considerable excess of the latter. Analysis of aliquot portions of the solution, maintained at 28·5°, showed that after 1 hour 96·5% of the arsenic was present as arsenic acid, and after 1·5 hours this oxidation was complete. Furthermore, when standard aqueous solutions of arsenious acid and of excess of chloramine-T were mixed at 28·5°, complete oxidation of the arsenic to arsenic acid had occurred within 5 minutes. This reaction is indeed sufficiently rapid to enable arsenious acid to be estimated accurately by titration with a standard chloramine-T solution, provided the arsenious acid solution be warmed before titration (cf. Noll, *Chem.-Ztg.*, 1924, **48**, 845; McMillan and Easton, *J. Soc. Chem. Ind.*, 1927, **46**, 472T).

These results harmonise with those obtained in the phosphine series, since it is the *corresponding* stages C and E in the phosphine and the arsine series respectively which are so rapid; in the arsine series, however, there is no stable intermediate compound corresponding to hypophosphorous acid, the oxidation of which delays so markedly the complete reaction in the phosphine series. Hence, although stage D in the arsine series is slower than stage E, it is far more rapid than the sum of stages A and B in the phosphine series, and the complete oxidation of the arsine is therefore a very much more rapid process than that of the phosphine.

It should be borne in mind that the stages A and D in the phosphine and the arsine series are merely the first stages experimentally detectable: we have no knowledge of the unstable and highly reactive intermediate compounds that must be formed during these particular oxidation stages; *e.g.*, the true *initial* reactions may be oxidation to the compounds $H_3P\rightarrow O$ and $H_3As\rightarrow O$ respectively. On the other hand, it is noteworthy that when arsine was passed into the large excess of aqueous chloramine-T, the *p*-toluenesulphonamide precipitated as oxidation proceeded was at first coloured faintly brown in the neighbourhood of the incoming gas by the deposition of a trace of elementary arsenic, which, however, rapidly dissolved when the solution was more vigorously agitated. This indicates that elementary arsenic may be a direct, or alternatively a subsidiary, intermediate in stage D, and that it is then immediately oxidised to arsenious and arsenic acid. This oxidation of elementary arsenic is certainly possible, for a colloidal solution of arsenic, prepared by oxidation of arsine in aqueous solution by dissolved and atmospheric oxygen, was immediately decolorised by addition of aqueous chloramine-T.

Experimental.

The chloramine-T was commercial material which had been recrystallised from water and air-dried; analysis showed it to be the pure trihydrate and all weights recorded for this substance refer to this hydrate. When consistent titrations have been obtained in an analysis, only one value is given; in other cases, multiple values are given to indicate the order of agreement obtainable.

***Oxidation** of Hydrogen Sulphide.*—(1) *With excess of hydrogen sulphide.* A current of the gas, washed with water, was passed through a solution of chloramine-T (10·00 g.) in water (150 c.c.) at 15° until no further reaction was apparent. The precipitated *p*-toluenesulphonamide (5·60 g.), recrystallised from water to remove a trace of sulphur, had m. p. 137°; the original filtrate, treated with barium chloride and hydrochloric acid, gave barium sulphate (1·82 g.). The yields of sulphonamide and barium sulphate are 92·1 and 87·9% of those required by equation (A), calculated on the weight of chloramine-T used.

(2) *With excess of chloramine-T.* (*a*) Potassium iodide–starch as an external indicator. 50 C.c. of a chloramine-T solution containing 11·905 g./l. were titrated with a standard hydrogen sulphide solution containing 1·12 g./l., the indicator being used externally. Only a faint opalescence of sulphur was formed, and at the end-point the only acid component detected in the solution was sulphuric acid. Volume of hydrogen sulphide required = 18·1 c.c. Hence 1 g.-mol. of hydrogen sulphide has been oxidised by 56·8 g. of oxygen. The low result (calc.: 64 g.) is probably due primarily to loss of hydrogen sulphide during manipulation, and to a much smaller extent to the slight formation of elementary sulphur. When, on the other hand, the hydrogen sulphide solution was titrated with the chloramine-T, the loss of hydrogen sulphide was considerable, and erratic end-points made the analysis worthless.

(*b*) Potassium iodide–starch as an internal indicator. 25 C.c. of the hydrogen sulphide solution were placed in a stoppered bottle, a 10% solution of potassium iodide (3 drops) and starch solution (2 c.c.) added, and the mixture titrated with the chloramine-T solution until a faint permanent blue colour was obtained, the bottle being kept stoppered between additions of the chloramine-T. Much sulphur was deposited and only a trace of sulphuric acid was formed. Volume of chloramine-T required = 18·1 c.c. Hence 1 g.-mol. of hydrogen sulphide has been oxidised by 14·8 g. of oxygen (calc. for oxidation to sulphur: 16 g.). Consistent values were obtained only after experience with this titration: earlier experiments gave a series of titration values showing considerable mutual inconsistency.

To determine whether the iodide ion was responsible for this result, the experiment was repeated, but now 3 drops of 10% potassium bromide solution were used instead of the iodide and starch, and the titration was conducted with the iodide–starch indicator used externally. At the end-point, which was very indefinite, the solution contained only traces of sulphur and sulphuric acid, but smelt of bromine. Volume of chloramine-T required = 44·3, 48·1, 44·7, 47·0 c.c.; mean, 46·0 c.c., corresponding to oxidation of 1 g.-mol. of sulphide by 37·6 g. of oxygen. In view of this anomalous result, the products of this reaction would clearly repay further investigation.

Oxidation of Sodium Sulphide.—10 C.c. of a solution of pure sodium sulphide (8·56 g. of Na_2S/l.) were titrated with the chloramine-T solution, potassium iodide–starch being used as an external indicator; the variation in the end-point, although reduced by adding a dilute solution of tartaric acid to the indicator, was considerable. Much sulphur was deposited. Volume of chloramine-T required = 23·0, 24·7, 23·0, 24·2, 24·2 c.c.; mean, 23·8 c.c.; 1 g.-mol. of sodium sulphide therefore requires 14·7 g. of oxygen (calc. for equation B: 16 g.). When the above conditions were reversed, sodium sulphide being added to the chloramine-T, sulphur was again deposited, the excess of chloramine-T apparently not affecting the oxidation.

Oxidation of Sodium Sulphite.—(*a*) 20 C.c. of a sodium sulphite solution (containing 6·02 g. of Na_2SO_3/l.), diluted with a 10% solution of potassium iodide (3 drops) and starch solution (1 c.c.), were titrated with a chloramine-T solution containing 12·71 g./l. Volume of latter required = 20·1 c.c. Therefore, on the basis of equation (C), the sodium sulphite contains 5·73 g./l. (*b*) The titration was now reversed, 20 c.c. of the chloramine-T being titrated with sulphite. Volume of latter required = 18·95 c.c., whence sodium sulphite = 6·01 g./l.

Oxidation of Sodium Thiosulphate.—Initial experiments showed that when the thiosulphate was titrated with chloramine-T, potassium iodide–starch being used as an internal indicator, the end-point was very difficult to detect. When a small excess of acetic acid was added to neutralise the alkali formed, better results were obtained, but the end-point was still reached slowly and was indistinct. The best results were finally obtained thus: 20 c.c. of a solution of sodium thiosulphate, containing 8·21 g. of sodium thiosulphate/l. (by analysis), were titrated with the chloramine-T solution (12·71 g./l.) almost to the end-point; the potassium iodide and starch were then added as in the sulphite estimation, and also tartaric acid (1 g.), and the titration continued, a fairly sharp end-point being now obtained. Volume of chloramine-T solution required = 12·5, 12·55, 12·4 c.c.; mean, 12·5 c.c. Hence 1 mol. of sodium thiosulphate requires 0·54 mol. of chloramine-T, and the reaction is in accordance with equation (D).

Phosphine.—This gas was prepared by the action of dilute sulphuric acid on aluminium phosphide, and was washed by bubbling through cold, freshly boiled, distilled water. It was not spontaneously inflammable and was free from other phosphorus hydrides.

Estimation of Phosphoric Acid.—In the following experiments, it was necessary to estimate phosphoric acid in a solution containing hypophosphorous and phosphorous acids and chloramine-T, and for which, since the solution could be neither boiled nor treated with nitric acid, the usual phosphomolybdate method could not be employed. In the experiments at 28·5° the uranyl acetate method was therefore adopted, sodium salicylate being used as an indicator (Duparc and Rogovine, *Helv. Chim. Acta*, 1928, **11**, 598): a satisfactory end-point could be obtained by titration in the cold, instead of using hot solutions as these authors recom-

mended. The uranyl acetate solution was therefore standardised by titration with a known solution of A.R. disodium hydrogen phosphate, and then used for the phosphate estimation under strictly parallel conditions. The accuracy of the method was proved by the fact that when oxidation was complete in the following experiments, and the total phosphate was then estimated both volumetrically by the uranyl acetate method and gravimetrically by the phosphomolybdate method, almost identical results were obtained. For the experiments at 38·5°, Fiske and Subbarow's colorimetric method of phosphate estimation (*J. Biol. Chem.*, 1925, **66**, 375) was used, its reliability under these conditions having previously been carefully checked.

Oxidation of Phosphine.—(a) *Excess of phosphine.* A stream of phosphine was passed into a solution of chloramine-T (5 g.) in water (100 c.c.) until the solution smelt markedly of phosphine and gave no reaction for unchanged chloramine-T (tested externally with potassium iodide and acetic acid). The white precipitate was collected, washed, and dried, and found to be *p*-toluenesulphonamide. The filtrate contained hypophosphorous and phosphorous acids but only a faint trace of phosphoric acid. The experiment was repeated with an alcoholic solution of chloramine-T; identical results were obtained except that the sulphonamide now remained in solution.

(b) *Excess of chloramine-T.* The phosphine was passed into a solution of chloramine-T (30·0 g.) in freshly boiled, cold, distilled water (500 c.c.) for 15 minutes. The mixture was then filtered, the residual *p*-toluenesulphonamide washed with water, and the united filtrate and washings diluted to 2000 c.c. with water at *ca.* 30° and placed in a thermostat at 28·5°. Samples (100 c.c.) were withdrawn periodically, and the phosphoric acid content determined volumetrically by the uranyl acetate method. Meanwhile, the total phosphorus in one sample was oxidised to phosphoric acid by boiling with nitric acid, and the phosphoric acid then determined gravimetrically as phosphomolybdate. The percentage of total phosphorus converted into phosphoric acid at known intervals was thus calculated (curve I). This phosphate content was 95·8% after 146·5 hours, and 98·5% after 169·0 hours; when oxidation was complete, the total phosphoric acid concentration was 0·975 g./l.

Oxidation of Sodium Hypophosphite.—(a) *Neutral solution.* Solutions of sodium hypophosphite, NaH_2PO_2,H_2O (3·68 g.), and chloramine-T (30·0 g.), each in water (750 c.c.), were mixed and diluted to 2000 c.c., water at the thermostat temperature (28·5°) being used throughout. The solution was at once placed in the thermostat, and the experiment then performed exactly as in (b) above, except that the quantity of sulphonamide separating at this dilution was so small that filtration was unnecessary. Curve II was thus obtained. In this case, the phosphate content was 92·0% after 168·0 hours and 99·8% after 192·0 hours, demonstrating the accuracy of the analytical methods employed. The total phosphoric acid concentration was finally 1·695 g./l.

(b) *Acid solution.* The following solutions were prepared in water at 28·5° : sodium hypophosphite (4·20 g. in 500 c.c.), acetic acid (2·3 c.c., 1 mol., in 20 c.c.), and chloramine-T (30·0 g. in 500 c.c.). The first and second were mixed and then added to the third, and the total volume made up to 2000 c.c. The experiment was precisely similar to the previous one, except that the presence of the acid caused a slight deposition of the sulphonic chloro-amide; this rapidly settled, but the aliquot portions were withdrawn through a filter-plug to avoid unnecessary contamination. Curve III was thus obtained. The phosphate content was now 97·0% after 144 hours and 99·5% after 184 hours, the total phosphoric acid concentration being finally 1·900 g./l.

Oxidation of Sodium Phosphite.—(a) *Neutral solution.* Solutions of disodium phosphite, $Na_2HPO_3,5H_2O$ (3·60 g.), and of chloramine-T (30·00 g.), each in water (500 c.c.) at 28·0°, were mixed, and the solution diluted to 2000 c.c. with water also at 28·0°. The solution was maintained at this temperature, but even after 24 hours only a trace of phosphate had been formed.

(b) *Acid solution.* This experiment was repeated, but the solution of disodium hydrogen phosphite (4·040 g.) in water (500 c.c.) was diluted with acetic acid (2·1 c.c., 2 mols.) before addition of the chloramine-T solution. A small precipitate of the chloro-amide now appeared and was removed by a filter-plug before analysis as in the oxidation of sodium hypophosphite (b). After 0·5 hour, the concentration of phosphate (calculated as phosphoric acid) was 0·799 g./l., representing an 84·4% conversion of total phosphorus into phosphate, and after 1·0 hour the concentration was 0·943 g./l., representing a 99·6% conversion. No further increase occurred. The total phosphate concentration (after oxidation with nitric acid) was 0·947 g./l.

Arsine.—The gas was prepared by the action of dilute sulphuric acid on aluminium arsenide, and washed with cold, freshly boiled, distilled water.

Estimation of Arsenate with Uranyl Acetate Solution.—It was found that arsenates in solution could be determined by precisely the same method as that adopted for phosphates. To test the accuracy of this method, 50 c.c. of a standard solution of arsenic acid were diluted with water (50 c.c.) and with a 10% sodium salicylate solution (10 c.c.), and then titrated in the cold with a solution of uranyl acetate (*ca.* 12·2 g./l.) until a permanent faint pink colour remained after 30 seconds' vigorous shaking. It was thus found that 100 c.c. of the acetate solution ≡ 0·440 g. of H_3AsO_4. An arsenic acid solution of unknown strength was then titrated with the uranyl acetate solution under precisely similar conditions. Volume of uranyl acetate solution required for 50 c.c. of the arsenic acid solution = 25·1 c.c. Therefore concentration of this arsenic acid solution = 2·20 g./l. This solution was then standardised by diluting aliquot portions with a large excess of concen-

trated hydrochloric acid, followed by an excess of 10% potassium iodide solution, the liberated iodine being titrated with standard sodium thiosulphate solution. The arsenic acid solution was thus found to contain 2·25 g./l.

Estimation of Total Arsenic in a Solution containing Arsenious and Arsenic Acids, Chloramine-T, and Sodium Chloride.—Some of the solutions in the following experiments contained comparatively large quantities of chloramine-T, the greater part of which it was considered desirable to remove before estimating the arsenic. Concentrated nitric acid was therefore added to the chilled solution to precipitate *p*-toluenesulphonchloro-amide, $C_6H_4Me{\cdot}SO_2{\cdot}NHCl$, and the solution was then filtered and the residual chloro-amide washed repeatedly with cold water. The united filtrate and washings were further acidified and then treated with an excess of 2% aqueous silver nitrate solution. The solution was again filtered and the silver chloride washed as before on the filter. The filtrate was then treated with a slight excess of sodium acetate in order to precipitate silver arsenite and arsenate. The latter were collected, washed repeatedly with water, dissolved in the minimum quantity of 50% nitric acid, and the silver then estimated by Volhard's method. In the above circumstances, it is probable that the nitric acid would oxidise much of the arsenious to arsenic acid: in any case, however, both acids would be precipitated as their trisilver ortho-salts, and total arsenic can be calculated as arsenate on the basis that $3Ag \equiv H_3AsO_4$.

Oxidation of Arsine.—(a) *Excess of arsine.* Arsine was passed into a cold solution of chloramine-T (4·00 g.) in water (200 c.c.) until all reaction was complete (*ca.* 50 mins.) and the solution had a marked odour of arsine; the surface of the solution finally developed a trace of elementary arsine owing presumably to atmospheric oxidation. After standing in a closed vessel for 20 mins., the solution was filtered to remove sulphonamide, the latter washed, and the filtrate diluted to 500 c.c. Analysis of aliquot portions by the above methods showed that the filtrate contained 0·497 g. of free arsenic acid, and total arsenic present was equivalent to 0·504 g. of arsenic acid. Theoretical yield of arsenic acid from the chloramine-T ≡ 0·500 g.

(b) *Excess of chloramine-T.* Arsine was passed into a solution of chloramine-T (30·0 g.) in water (400 c.c.) at 20° for 25 mins. Precipitated sulphonamide was removed, and the filtrate diluted to 1 l. with water at 28·5° and placed in a thermostat at this temperature. After 1 hour the free arsenic acid present was 0·502 g. and after 1·5 hours 0·520 g.; the total arsenic present was found to equal 0·520 g. of arsenic acid. The value after 1 hour corresponds to a 96·5% conversion of total arsenic into arsenic acid.

Oxidation of Arsenious Acid.—(a) Solutions of A.R. arsenious oxide (2·450 g.) and of chloramine-T (7·5 g.) in water (500 and 200 c.c.), each at 28·5°, were mixed, and the total volume made up to 1 l. with water at 28·5°. Within 5 mins. of mixing, the solution contained 3·52 g. of free arsenic acid, determined by the uranyl acetate method. Since the arsenious oxide should have given 3·516 g. of arsenic acid, complete oxidation had occurred in this period. It is possible that the oxidation is even more rapid, but the method did not allow of more rapid determinations.

(b) To use this oxidation analytically, 50 c.c. of a solution containing 1·520 g./l. of A.R. arsenious oxide were heated on a water-bath for 5 mins. and then titrated with a solution containing 11·900 g./l. of chloramine-T, the end-point being determined externally with potassium iodide–starch paper. Volume of chloramine-T solution required = 18·0 c.c. Hence the original solution contained 1·51 g./l. of arsenious oxide.

Oxidation of Colloidal Arsenic.—The arsine, prepared and washed as above, was passed into cold distilled water containing dissolved air until a marked formation of brown "colloidal" arsenic had occurred. The addition of a 10% solution of chloramine-T, followed by shaking, gave immediately a colourless, transparent solution.

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28. *The Amino-derivatives of Pentaerythritol. Part II. The Thermal Decomposition of the Tetrahydrochlorides of Tetrakismethylaminomethylmethane and of Tetrakisdimethylaminomethylmethane.*

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Thermal decomposition of the tetrahydrochloride of the methylamino-base gives the dihydrochloride of αγ-bismethylaminopropane (I) by simple fission of the molecule. That of the tetrahydrochloride of the dimethylamino-base is entirely different and yields the hydrochloride of an amine $C_9H_{18}N_2$, which has been shown to have the structure (III), and thus to be constitutionally analogous to β-methylglutaconic acid. This base has many interesting properties, in particular, the low reactivity of its double bond, its ready hydrogenation to *iso*butane, and the abnormal behaviour of its quaternary salts with silver oxide. An attempted synthesis of the dimethiodide of this base gave a product which proved to be the second geometric isomeride. The properties of these various amino-derivatives have been studied in detail.

In Part I (Litherland and Mann, J., 1938, 1588) the synthesis of tetrakisaminomethylmethane, $C(CH_2{\cdot}NH_2)_4$, and its subsequent methylation to the octamethyl derivative $C(CH_2{\cdot}NMe_2)_4$ were described, and it was shown that the reaction of the latter compound with methyl iodide was abnormal, since under the usual conditions of quaternary salt formation only a dimethiodide, $C(CH_2{\cdot}NMe_2)_2(CH_2{\cdot}NMe_3I)_2$, was formed. This, however, underwent thermal decomposition just above its m. p., with formation of the quadri-quaternary iodide, $C(CH_2{\cdot}NMe_3I)_4$.

The latter reaction is also so abnormal that an investigation of the thermal decomposition of several other quaternary alkyl halide derivatives of the octamethyl base has been undertaken (see Part III, following paper). A necessary preliminary investigation, however, was that of the thermal decomposition of the tetrahydrochloride of the octamethyl base, now to be described, together with the results of a simpler investigation.

When the tetrahydrochloride of tetrakismethylaminomethylmethane, $C(CH_2{\cdot}NHMe,HCl)_4$, prepared by van Alphen's method (*Rec. Trav. chim.*, 1938, **57**, 265), was heated just above its m. p., decomposition occurred with formation of the *dihydrochloride* of *αγ-bismethylaminopropane* (I), the identity of which has been confirmed by direct synthesis. It is clear that this reaction is essentially merely the fission of two of the side chains from the original molecule:

$$(HCl,NHMe{\cdot}CH_2)_2C(CH_2{\cdot}NHMe,HCl)_2 \longrightarrow CH_2(CH_2{\cdot}NHMe,HCl)_2 \quad \text{(I.)}$$

It should be emphasised that this is a reaction only of the salt, the free tetramethyl base being volatile without decomposition.

When, however, the hydrated tetrahydrochloride of the octamethyl base, $C(CH_2{\cdot}NMe_2,HCl)_4$, $3H_2O$, was heated at 232—233°, *i.e.*, just above its m. p., a brisk evolution of formaldehyde occurred, and the residual syrup was found to contain the hydrochlorides of mono-, di-, and tri-methylamine and of an *amine* of molecular formula $C_8H_{18}N_2$. The mode of decomposition of the tetrahydrochloride of the octamethyl base is thus entirely different from that of the corresponding tetramethyl base. The amine $C_8H_{18}N_2$, which will be referred to as the " pyro "-base, has considerable stability and can be distilled unchanged at atmospheric pressure; its dihydrochloride can be sublimed unchanged.

The constitution of the " pyro "-base rests on the following evidence:

(1) It is a di-tertiary amine, and readily formed a *dimethiodide*, etc.

(2) Catalytic reduction at room temperature of the amine *dihydrochloride* in aqueous or alcoholic solution readily occurred with absorption of 3 mols. of hydrogen and the production of *iso*butane and dimethylamine: the dimethiodide similarly gave *iso*butane and trimethylamine. It follows therefore that the " pyro "-base must have the constitution (II), (III), or (IV).

$CH_2{:}C(CH_2{\cdot}NMe_2)(CH_2{\cdot}NMe_2)$ (II.)

$CH_3{\cdot}C(CH{\cdot}NMe_2)(CH_2{\cdot}NMe_2)$ (III.)

$CH_3{\cdot}CH(CH{\cdot}NMe_2)(CH{\cdot}NMe_2)$ (IV.)

Attempts to arrest the hydrogenation when only 1 or 2 mols. of hydrogen had been absorbed gave unchanged material and the above reduction products, and the intermediate reduction products, whose nature would have furnished valuable evidence for the structure of the " pyro "-base, could not be isolated. The " pyro "-base did not undergo this ready hydrogenation, and was also unaffected by other reducing agents, *e.g.*, sodium and alcohol.

(3) Of the above three possibilities for the " pyro "-base, the compound (II) could clearly be produced most simply from the octamethyl hydrochloride. The following evidence shows almost conclusively that the structure (II) is incorrect.

(*a*) The " pyro "-base and its salts are very stable compounds and lack many of the properties of unsaturated compounds; *e.g.*, the quaternary salts of the base were unaffected by bromine or iodine in aqueous or alcoholic solution, and the dihydrochloride in aqueous solution was unaffected by small quantities of bromine and gave solely an orange perbromide with excess of bromine. The free base is rather more reactive than its derivatives, and in chloroform solution it reacted with bromine, with the production, however, of the *dihydrobromide* of the unchanged base, no other crystalline derivative being isolated. [This result recalls Thorpe's inability (J., 1919, **115**, 680) to obtain any definite product from the action of bromine on the " normal " form of β-methylglutaconic acid of m. p. 149°, which apart from the terminal groups has the same structure as the base (III).] Furthermore, the *dimethochloride* in aqueous or acetic acid solution did not undergo ozonolysis. This lack of reactivity of the double bond would be expected in (III), but certainly not in (II). The free base of conventional formula (III) would actually exist as a resonance hybrid between (III) and (III A), and would therefore have greater

stability and less reactivity than formula (III) implies. The simple and quaternary salts cannot show this resonance. In these compounds, however, the positive poles on the nitrogen atoms must act as

(IIIA.) $CH_3\cdot\bar{C}\langle^{CH:\overset{+}{N}Me_2}_{CH_2\cdot NMe_2}$ $\qquad$ $CH_3\rightarrow C\langle^{CH\rightarrow\overset{+}{N}Me_3I}_{CH_2\rightarrow\overset{+}{N}Me_3I}$ (IIIB.)

vigorous electron-attractors: this attraction by the upper nitrogen atom (III B), which is further reinforced by the inductive effect of the methyl group, will cause a neutralisation of the polarity of the adjacent double bond, and thus render this bond only feebly active to cationoid reagents such as bromine. These factors in the quaternary salts are presumably more potent than the resonance factor in the free base.

(*b*) Since the reactivity of the double bond in (II) cannot be markedly affected by the nitrogen atoms, the first stage in catalytic reduction would be saturation of this bond with the formation of *αγ-bisdimethylamino-β-methylpropane*, $CH_3\cdot CH(CH_2\cdot NMe_2)_2$. This compound has now been synthesised by the action of dimethylamine on αγ-dibromo-β-methylpropane, and its *dimethiodide* could not be catalytically reduced under the previous conditions. It follows that this dimethiodide cannot be an intermediate in the catalytic reduction of the dimethiodide of the " pyro "-base. Reduction of the compound (III), however, would probably remove first the lower NMe_2 group, and then, since the stability of the double bond would thus be (if anything) enhanced, would next remove the upper NMe_2 group before final reduction to *iso*butane. Some evidence for the priority of the first of these stages is provided by Mannich, Handke, and Roth (*Ber.*, 1936, **69**, 2116), who showed that αγ-bisdimethylamino-Δ^{α}-butene, $NMe_2\cdot CH{:}CH\cdot CHMe\cdot NMe_2$, on catalytic reduction at 40° gave a mixture of α-dimethylamino- and αγ-bisdimethylamino-butane and dimethylamine.

(*c*) Even if the compound (II) were initially formed, at the high temperature of the reaction it would probably undergo rapid conversion into (III), since during the formation of olefins at high temperatures the double bond usually adopts that position which gives the most highly substituted ethylene.

(4) Oxidation of the " pyro "-base quaternary salts by alkaline permanganate gave formaldehyde and oxalic acid. The formaldehyde was undoubtedly obtained from the $-\overset{+}{N}Me_3$ groups, several similar examples being known. The production of oxalic acid does not differentiate between (II) and (III). The amine (II), on oxidative fission of the double bond, should give mesoxalic acid and hence finally oxalic acid. The amine (III), on similar fission, should give pyruvic acid. Now the latter is known to yield oxalic acid on oxidation with nitric acid (Böttinger, *Annalen*, 1877, **188**, 299; Œschsner de Coninck, *Bull. Acad. roy. Belg.*, 1905, 524): we find that pyruvic acid on treatment with alkaline permanganate under the above conditions gives oxalic acid in 90% yield, the pyruvic acid therefore reacting presumably in the enolic form, $CH_2{:}C(OH)\cdot CO_2H$.

(5) The possibility that the " pyro "-base is 2 : 3-bisdimethylamino-1-methyl*cyclo*propane (IV) could not be excluded, as the *cyclo*propane ring is known sometimes to be formed from the pentaerythritol skeleton (Litherland and Mann, *loc. cit.*). This structure is exceedingly unlikely, as the production of *iso*butane would involve fission of the ring between carbon atoms 2 and 3, and that of oxalic acid would involve a double fission between carbon atoms 1 and 2, and 1 and 3. Furthermore, the high-temperature formation of the " pyro "-base would almost certainly have given the most stable form of the base, which in (IV) would probably have the dimethylamino-groups in the *trans*-position and thus enable the molecule to show optical activity. Attempts to resolve the amine or its quaternary salts failed, however.

(6) The synthesis of a compound of structure (III) was therefore attempted. *s*-Dichloroacetone was converted by methylmagnesium bromide into *αγ-dichloro-β-methyliso**propyl** alcohol* (VI), which, heated with dimethylamine gave *αγ-bisdimethylamino-β-methyliso**propyl** alcohol* (VII), but all attempts to dehydrate (VII) and so obtain the required compound (III) failed. The amine (VII) was therefore

$$\underset{\text{(VI.)}}{CMe(OH)(CH_2Cl)_2} \longrightarrow \underset{\text{(VII.)}}{CMe(OH)(CH_2\cdot NMe_2)_2} \longrightarrow \underset{\text{(VIII.)}}{CMeCl(CH_2\cdot NMe_2)_2} \longrightarrow \underset{\text{(IX.)}}{CMe(OEt)(CH_2\cdot NMe_2)_2}$$

$$\text{(X.)}\ CMeCl(CH_2\cdot NMe_3I)_2 \longrightarrow MeC\langle^{CH\cdot NMe_3I}_{CH_2\cdot NMe_3I}\ \text{(XI.)}$$

converted by thionyl chloride into *β-chloro-αγ-bisdimethylamino-β-methylpropane* (VIII), from which, however, hydrogen chloride could not be eliminated, alcoholic potash in particular giving the *β-ethoxy*-compound (IX). The chloro-compound (VIII) was therefore converted into its *dimethiodide* (X), which when treated with 1 equiv. of potassium hydroxide readily gave *αγ-bistrimethylammonium-β-methylpropenylene di-iodide* (XI), *i.e.*, the dimethiodide of (III). The elimination of hydrogen chloride would

almost certainly proceed as indicated, and would not have involved the methyl group to give the highly reactive $CH_2{:}C{=}$ grouping : this is confirmed further by the fact that this elimination is controlled by the positive charge on the nitrogen atom, which would obviously influence a neighbouring rather than a distant hydrogen atom. These synthetic results are in close harmony with those of Ingold and Rothstein (J., 1931, 1666), who were unable to dehydrate the compound $CH(OH)(CH_2{\cdot}NEt_2)_2$ or to eliminate hydrogen chloride from $CHCl(CH_2{\cdot}NEt_2)_2$, but found that the dimethiodide of the latter was smoothly converted by alcoholic potash into $[NEt_2Me{\cdot}CH{:}CH{\cdot}CH_2{\cdot}NEt_2Me]I_2$.*

It was found, however, that the synthetic methiodide (XI) had m. p. 203—204°, and the " pyro "-base methiodide m. p. 216—217°, whereas a mixture had m. p. 206—210°; furthermore, the *dimethopicrate* obtained from (XI) had m. p. 245—246°, that from the " pyro "-base m. p. 257—257·5°, and a mixture m. p. 250—253°. *X*-Ray powder photographs of the two methiodides, kindly taken by Mr. H. S. Peiser, showed conclusively that the two compounds were not identical. The closeness of each of the above pairs of m. p.'s, and the intermediate value of each mixed m. p., indicate, however, that the two compounds in each pair must be chemically closely allied. Evidence that the difference between the two methiodides is in fact stereochemical and not structural, *i.e.*, that they are geometric isomerides, is provided by the following reactions :

(*a*) The synthetic dimethiodide (XI) also underwent smooth catalytic reduction at room temperature with absorption of 3 mols. of hydrogen to give *iso*butane and 2 mols. of trimethylammonium iodide. On oxidation with alkaline permanganate it also gave oxalic acid.

(*b*) Both dimethiodides when boiled with alcoholic potash underwent decomposition with liberation of all their nitrogen as trimethylamine. When, however, they were boiled in aqueous solution with an excess of silver oxide, only 1 mol. of trimethylamine was liberated, and the solution then contained the ion $[C_{14}H_{30}N_2O]^{++}$ (XIV); this was isolated as the *dipicrate*, *dichloroaurate*, and *chloroplatinate*, the same dipicrate being obtained from both dimethiodides. The mechanism of this reaction is uncertain. The first product of the action of the silver oxide, *viz.*, the dihydroxide (XII), cannot undergo normal quaternary ammonium hydroxide decomposition at either pole, since this would involve loss of trimethylamine and the removal of a β-hydrogen atom as a molecule of water by the hydroxyl ion. In such circum-

$CH_3{\cdot}C\lessdot{}^{CH{\cdot}NMe_3{\cdot}OH}_{CH_2{\cdot}NMe_3{\cdot}OH}$ (XII.) $\quad$ $CH_3{\cdot}C\lessdot{}^{CH{\cdot}NMe_3{\cdot}OH}_{CH_2{\cdot}OH}$ (XIII.) $\quad$ $[\overset{+}{N}Me_3{\cdot}CH{:}CMe{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}\overset{+}{N}Me_3]$ (XIV.)

stances, formation of the alcohol (XIII) would be expected; actually, the corresponding ether (XIV) is formed. It is very unlikely that the trimethylamine arose from the upper nitrogen atom in (XII), as this would have produced an aldehyde which would, in turn, have been oxidised to an acid. The important fact is, however, not the structure of (XIV), but the production of this ion from both dimethiodides; evidently the most stable geometric isomer of (XIV) is ultimately obtained during the prolonged boiling with silver oxide. This ether formation during quaternary ammonium hydroxide decomposition is, however, not unique, although very rare : Gabriel and Colman (*Ber.*, 1906, **39**, 2875) have shown that 1 : 1-trimethylenepiperidinium hydroxide, when heated with aqueous potassium hydroxide, gives di-γ-piperidino-*n*-propyl ether, $(C_5H_{10}N{\cdot}[CH_2]_3)_2O$.

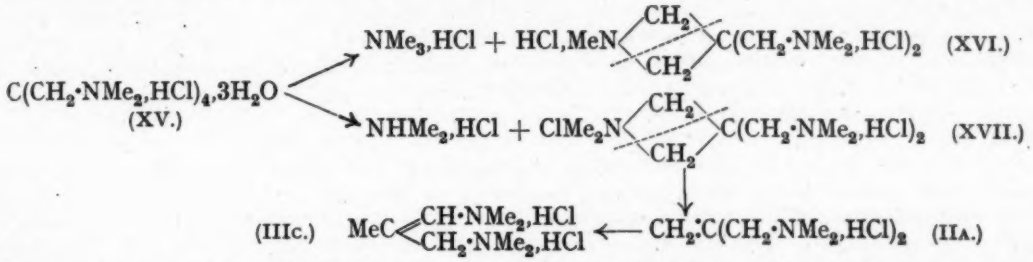
(*c*) There is some evidence of slow interconversion of the quaternary salts of the " pyro "-base and the synthetic salts at room temperature. A sample of the crystalline " pyro "-base dimethochloride was kept in a securely stoppered tube for 2 years, by which time it had liquefied. When this was boiled in aqueous solution with silver oxide for a short time, and the product precipitated as the picrate, recrystallisation ultimately gave the pure, slightly soluble *dipicrate* of the synthetic salt. The liquefaction was apparently caused by the formation of a mixture of the two dimethochlorides, from which the " pyro "-component was preferentially removed by the silver oxide, the action of the latter being stopped before the second isomeric component had been completely decomposed. This interconversion at room temperature was not observed in any other salt.

Since there is no evidence as to which of the dimethiodides has the *cis*- and which the *trans*-structure, it is proposed for future reference to call the " pyro "-base and its derivatives the α-series, and the synthetic methiodide and its derivatives the β-series.

It should be noted that the synthesis of the dimethiodide (XI) also disposes of the *cyclo*propane structure (IV), since there is no rational mechanism by which the elimination of hydrogen chloride from (X) could give the *cyclo*propane ring.

* In view of the close analogy between the two syntheses at all stages, it is remarkable that Ingold and Rothstein's unsaturated dimethiodide on catalytic reduction gave solely the saturated $CH_3(CH_2{\cdot}NEt_2MeI)_2$, whereas our dimethiodide was reduced completely to *iso*butane.

With regard to the mechanism of the formation of the " pyro "-base from the octamethyl tetrahydrochloride, it is significant that several monoalkyl iodides of the octamethyl base readily undergo ring closure to form derivatives of ββ-bisdimethylaminomethyl-*N*-methyltrimethyleneimine (XVI), and that, furthermore, benzyl iodide under certain conditions causes complete disruption into " pyro "-base derivatives (see Part III). These reactions make it highly probable that the first stage of the decomposition of the hydrated tetrahydrochloride (XV) consists of two simultaneous reactions, (*a*) formation



of the hydrochlorides of trimethylamine and of (XVI) and (*b*) formation of dimethylamine hydrochloride and the methochloride (XVII) corresponding to (XVI). The ring in (XVI) then undergoes fission as shown in the presence of water to give formaldehyde, monomethylamine hydrochloride, and the unstable methylene base dihydrochloride (IIA), which then passes over into the very stable " pyro "-base dihydrochloride (IIIc). The ring in (XVII) by a similar fission gives the same products, except that di- instead of mono-methylamine is formed. The high yield of dimethylamine and low yield of mono- and tri-methylamine show that reaction (*b*) predominates over (*a*). In view of the close structural analogy between the " pyro "-base (III) and β-methylglutaconic acid, it is noteworthy that Goss, Ingold, and Thorpe (J., 1923, **123**, 327) emphasise " the remarkable tendency to the formation of the mobile glutaconic acids, which is such that groups, for instance $-CO_2Et$ groups, are removed with quite extraordinary ease, and in the presence of reagents which do not usually effect their elimination, when the mobile hydrogen atom necessary for glutaconic tautomerism can thereby be acquired." It is probable that this same tendency underlies the formation of the " pyro "-base and may thus be the dominant factor determining the course of the thermal decomposition.

Many attempts have been made to synthesise an amine of structure (IV) for direct comparison with the " pyro "-base, but all have failed. The preparation and isolation of the three isomeric 1-methyl-*cyclo*propane-2 : 3-dicarboxylic acids have been described by Goss, Ingold, and Thorpe (*loc. cit.*; see, however, Feist, *Annalen*, 1924, **436**, 125), but the isolation of the required pure *trans*-dicarboxylic acid in practicable quantities is exceedingly laborious. A mixture of pure diamides or dihydrazides could not be obtained by treating the esterified mixture of *cis*- and *trans*-acids with ammonia or hydrazine respectively. The Curtius degradation of the crude dihydrazide gave, however, 2 : 3-diamino-1-methyl-*cyclo*propane, isolated as the *dibenzoyl* derivative, but in spite of many variations in the conditions the yield was uselessly low, and methylation of this diamine was not attempted.

In the early stages of this investigation, when only salts of the " pyro "-base were available and its molecular weight was unknown, it appeared possible that the base was *N*-methyltrimethyleneimine. Trimethyleneimine, prepared by the method of Marckwald *et al.* (*Ber.*, 1898, **31**, 3264; 1899, **32**, 2031), when treated with methyl iodide in cold ethereal solution, gave the *hydriodide* of the unchanged base; when treated with methyl iodide and alcoholic potash it gave *N-methyltrimethyleneimine methiodide*. The insolubility of the latter in all liquids other than water indicated a possibility of polymerisation, however. It was of course quite distinct from the methiodide of the " pyro "-base.

Experimental.

Tetrakisaminomethylmethane, $C(CH_2·NH_2)_4$.—Van Alphen (*loc. cit.*) has described a monohydrate of this base, having b. p. 278—282°. We, however, ground the disulphate of the tetramine (see Part I, p. 1591) with much powdered potassium hydroxide, extracted the mixture several times with boiling benzene, and fractionally distilled the united filtered extracts; the amine boiled at 282—284° and solidified on cooling to an exceedingly deliquescent, waxy solid. This was recrystallised from benzene, and the *tetrahydrate* of the amine obtained as fine needles, m. p. 100—100·5° (Found : N, 26·9. $C_5H_{16}N_4,4H_2O$ requires N, 27·45%). This compound underwent slow dehydration to the monohydrate when kept over phosphoric oxide in a vacuum (Found : N, 37·0. Calc. for $C_5H_{16}N_4,H_2O$: N, 37·3%).

Tetrakismethylaminomethylmethane, $C(CH_2·NHMe)_4$.—This was prepared essentially by van Alphen's method (*loc. cit.*), a mixture of the tetrabromo-compound, $C(CH_2Br)_4$, (40 g.) and a 27% alcoholic methyl-

amine solution (240 c.c.) being heated at 170° for 9 hours. The excess of alcohol and methylamine was then distilled off, and the residue evaporated almost to dryness and treated with much powdered potassium hydroxide. The base was extracted with ether and dried (potash); fractional distillation then gave a *dihydrate* of the tetramethyl-base, of b. p. 245—248°, as a colourless viscous liquid (Found: N, 25·4. $C_9H_{24}N_4,2H_2O$ requires N, 25·0%); yield 11 g. (55%). According to van Alphen, this procedure should give a hemihydrate, b. p. 235—238°. The tetramethyl base gave the monohydrated *tetrahydrochloride*, colourless crystals from alcoholic hydrochloric acid, m. p. 264° (decomp.) (Found: C, 30·7; H, 8·3; N, 15·8; Cl, 40·4. $C_9H_{24}N_4,4HCl,H_2O$ requires C, 30·7; H, 8·5; N, 15·9; Cl, 40·35%), and the monohydrated *tetrahydrobromide*, similar crystals from alcoholic hydrobromic acid, m. p. 266° (decomp.) (Found: Br, 60·4. $C_9H_{24}N_4,4HBr,H_2O$ requires Br, 60·3%), which readily gave the anhydrous *salt* (Found: C, 20·8; H, 5·7. $C_9H_{24}N_4,4HBr$ requires C, 21·1; H, 5·5%). *Tetrakisbenzenesulphonmethylamidomethylmethane*, $C(CH_2{\cdot}NMe{\cdot}SO_2Ph)_4$, was obtained as colourless crystals from acetic acid, m. p. 239° (Found: C, 52·8; H, 5·5. $C_{33}H_{40}O_8N_4S_4$ requires C, 52·9; H, 5·4%).

αγ-Bismethylaminopropane and its Derivatives.—A mixture of trimethylene dibromide (30 g.) and 21% aqueous-alcoholic methylamine solution (160 c.c.) was heated at 120—130° for 8 hours. The excess of methylamine was then removed, and the residue acidified with hydrochloric acid, evaporated to dryness, and treated with potassium hydroxide. The liberated amines were extracted with ether, dried, and fractionally distilled, the αγ-bismethylaminopropane being obtained as a colourless liquid *monohydrate*, b. p. 141—144° (Found: N, 24·5. $C_5H_{14}N_2,H_2O$ requires N, 23·3%); the yield was low owing to considerable formation of bases of b. p. >200°. The *dihydrochloride*, colourless needles from methyl alcohol, had m. p. 262—263° (Found: C, 34·6; H, 9·5; N, 15·7; Cl, 40·9. $C_5H_{14}N_2,2HCl$ requires C, 34·3; H, 9·15; N, 16·0; Cl, 40·6%); the *dipicrate*, pale yellow needles from hot water, turning brown on standing, had m. p. 193—194° (Found: C, 36·3; H, 3·8; N, 20·0. $C_5H_{14}N_2,2C_6H_3O_7N_3$ requires C, 36·4; H, 3·6; N, 20·0%).

Thermal Decomposition of the Tetramethyl Tetrahydrochloride, $C(CH_2{\cdot}NHMe,HCl)_4$.—The powdered tetrahydrochloride (39 g.) was heated at 275° for 45 mins., *i.e.*, until effervescence ceased. The product was treated with potassium hydroxide, extracted with ether, and the extracts dried and distilled. After the ether and much readily volatile amine had been removed, distillation gave the following fractions: (i) b. p. 55—58°/28 mm., 1·5 g.; (ii) b. p. 58—64°/27 mm., 1·0 g.; (iii) b. p. 140—170°/25 mm., 3·5 g.; (iv) b. p. 180—185°/18 mm., 0·8 g. Fractions (i) and (ii) were united, treated with hydrochloric acid, and taken to dryness: the residue, washed with alcohol and recrystallised from methyl alcohol, gave the above αγ-bismethylaminopropane dihydrochloride, m. p. 257° (Found: C, 34·1; H, 9·4; N, 15·4; Cl, 40·3%). The dihydrochloride gave the dipicrate, m. p. 193—194°, unchanged by admixture with the above authentic sample, and also turning brown on standing. Fractions (iii) and (iv) contained chiefly the unchanged tetramethyl base. The low yields of the four fractions show that considerably more extensive decomposition must have occurred during the above heating. When the heating was extended to 1·5 hours to eliminate fractions (iii) and (iv), only very small yields of all fractions were obtained, and the further decomposition had evidently become more complete.

Tetrakisdimethylaminomethylmethane.—The following method of preparation is more expeditious than methylation of the primary tetramine (Litherland and Mann, *loc. cit.*). A mixture of tetrakisbromomethylmethane (90 g.), anhydrous dimethylamine (85 g., 8 mols.), and alcohol (300 c.c.) was heated in a rotating autoclave at 170° for 9 hours. The cold product was diluted with water and then heated to 100° to distil off the excess of dimethylamine. The residual solution was made strongly alkaline, and distilled in steam. The distillate, acidified with hydrochloric acid and evaporated, gave a semi-solid mass of the hydrated tetrahydrochloride, which crystallised when triturated with alcohol. Yield, 52 g. (51%). The free *tetrakisdimethylamino-base* was isolated in the usual way as a colourless liquid, b. p. 157°/45 mm., 248—249°/769 mm. (Found: C, 63·8; H, 13·0; N, 23·2. $C_{13}H_{32}N_4$ requires C, 63·9; H, 13·1; N, 23·0%). The free base remains unchanged in a closed vessel; the tetrahydrochloride very slowly decomposes under these conditions, as shown by a steady fall in m. p., but one recrystallisation usually gives the pure salt.

Thermal Decomposition of the Octamethyl Tetrahydrochloride, $C(CH_2{\cdot}NMe_2,HCl)_4,3H_2O$.—The tetrahydrochloride (120 g., divided into five batches) was heated in an oil-bath at 232—233° until the steady vigorous effervescence subsided (*ca.* 20 mins.); the heating was continued for a further 2—3 mins. (longer heating gave a brown product), and the mixture then allowed to cool. A sample of the gas evolved was dissolved in water and found to be solely formaldehyde, identified by smell and as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 166—167°. The cold solidified mixture, on recrystallisation from alcohol, gave the *dihydrochloride* of the "pyro"-base, colourless crystals, m. p. 260° (decomp. with partial sublimation) (Found: C, 44·9; H, 9·7; N, 12·8; ionised Cl, 33·0. $C_8H_{18}N_2,2HCl$ requires C, 44·7; H, 9·3; N, 13·0; Cl, 33·0%); yield 25 g. A sample of the alcoholic mother-liquor was evaporated to a syrup and this was shaken with aqueous sodium hydroxide and benzenesulphonyl chloride; the mixture was then extracted with ether, and the ether in turn extracted with dilute hydrochloric acid. The ether on evaporation left a syrup which, after solidification and recrystallisation from petrol, gave much pure benzenesulphondimethylamide, m. p. 45—47°, unchanged by admixture with an authentic sample. The hydrochloric acid extract was basified, extracted with ether, and the extract treated with methyl iodide; the small amount of precipitate was collected, recrystallised from aqueous alcohol, and identified as tetramethylammonium iodide, unaffected by heating to 300°

(Found : N, 7·0; I, 62·8. Calc. for $C_4H_{12}NI$: N, 7·0; I, 63·2%). The above experiment was repeated, the original syrup being now shaken with sodium hydroxide and *p*-toluenesulphonyl chloride; after extraction with ether, the aqueous solution on acidification gave a very small quantity of *p*-toluenesulphonmethylamide, which, crystallised from aqueous alcohol, had m. p. and mixed m. p. 77°. The production of methyl-, dimethyl-, and trimethyl-amine during the thermal decomposition was thus proved.

The free " pyro "-*base*, obtained by ether extraction of a mixture of the dihydrochloride, powdered potassium hydroxide, and a small quantity of water, was isolated as a colourless liquid, b. p. 150—154°, 50—54°/12 mm., miscible with water (Found : N, 19·7; *M*, by Hofmann's vapour-density method at 100°/196 mm., 157. $C_8H_{18}N_2$ requires N, 19·7%; *M*, 142). This base gave the following salts : *dihydrobromide*, from alcohol, m. p. 243° with darkening (Found : C, 31·7; H, 6·55; Br, 52·6. $C_8H_{18}N_2,2HBr$ requires C, 31·6; H, 6·6; Br, 52·6%); *dihyd. ·dide*, from alcohol, m. p. 203—205° with previous softening, depending on the rate of heating (Found : C, 23·6; H, 5·1; N, 7·15. $C_8H_{18}N_2,2HI$ requires C, 24·1; H, 5·0; N, 7·0%); *dipicrate*, yellow needles from water, m. p. 185·5—187·5° (Found : C, 40·5; H, 4·1; N, 18·6. $C_8H_{18}N_2,2C_6H_3O_7N_3$ requires C, 40·0; H, 4·0; N, 18·7%). When the dihydrochloride was heated at its m. p. a sublimate of unchanged material, m. p. 250° (decomp.), was obtained; this gave a picrate (Found : N, 18·6%), which after recrystallisation from water had m. p. 184—186°, unchanged by admixture with the above preparation.

The dihydrochloride was unaffected by boiling with dilute hydrochloric acid (1 : 1 by vol.) under reflux for 2·5 hours; when the boiling was continued for 12 hours, some decomposition occurred but no indication of hydrogen chloride addition to the unsaturated base could be obtained.

An aqueous solution of the dihydrochloride was treated with silver *d*-α-bromocamphor-π-sulphonate (2 mols.), the mixture boiled and filtered, and the filtrate taken to dryness. The glassy residue, twice recrystallised from alcoholic ethyl carbonate, gave colourless crystals of the *dibromocamphorsulphonate*, m. p. 170—176°, $[M]_D^{19°}$ 556° in water. These were recrystallised five times from *iso*heptyl alcohol, and then had m. p. 165—172°, $[M]_D^{9°}$ 544°; three further crystallisations from *n*-heptyl alcohol gave $[M]_D^{9°}$ 534°, and two more crystallisations led to m. p. 174—178°, $[M]_D^{13°}$ 536° (Found : C, 43·5; H, 6·6; Br, 20·65. $C_8H_{18}N_2,2C_{10}H_{15}O_4BrS$ requires C, 43·85; H, 6·6; Br, 20·85%). Since the bromocamphorsulphonate ion has $[M]_D^{22°}$ 278·7° in aqueous solution (Pope and Read, J., 1910, **97**, 2201), it appeared that no resolution was occurring. This was confirmed by treating an alcoholic solution of the last crop with a saturated alcoholic solution of calcium bromide, whereby the inactive dihydrobromide of the " pyro "-base was precipitated.

The " pyro "-base, treated with methyl iodide in methyl-alcoholic solution, readily gave the *dimethiodide*, colourless crystals from alcohol, m. p. 216—217° (decomp., with preliminary darkening) (Found : C, 28·0; H, 5·6; N, 6·6; I, 59·5. $C_{10}H_{24}N_2I_2$ requires C, 28·2; H, 5·6; N, 6·6; I, 59·6%). An aqueous solution of this compound was shaken with excess of silver oxide, filtered, acidified with hydrochloric acid, and evaporated to a syrup, which solidified when treated with alcoholic acetone; recrystallisation from this mixed solvent gave colourless crystals of the *dimethochloride monohydrate* (Found : Cl, 27·15. $C_{10}H_{24}N_2Cl_2,H_2O$ requires Cl, 27·2%). This dimethochloride when heated melted at 184—186° with slight effervescence, then resolidified and again melted at *ca.* 200°; when heated at 130° for some time, it had m. p. 224° (decomp.). It is possible, therefore, that the preliminary heating gave the anhydrous material, which then had a sharp m. p.

The dimethochloride gave a *dichloroaurate*, m. p. 237—238·5° (decomp.) (Found : N, 3·5; Au, 46·2. $C_{10}H_{24}N_2Cl_8Au_2$ requires N, 3·3; Au, 46·4%), and a *chloroplatinate*, m. p. 245° (decomp.) (Found : C, 20·3; H, 4·7; N, 4·8; Pt, 32·6. $C_{10}H_{24}N_2Cl_6Pt,H_2O$ requires C, 20·1; H, 4·35; N, 4·5; Pt, 32·6%). The *dimethopicrate*, obtained from the dimethiodide and recrystallised from water, had m. p. 257—257·5° (decomp.) (Found : N, 17·8. $C_{22}H_{28}O_{14}N_8$ requires N, 17·8%).

The *dimetho*-d-*camphorsulphonate*, prepared from the dimethiodide in the usual manner, was crystallised repeatedly from acetone containing a small quantity of alcohol and finally had m. p. 261—263° with slight preliminary softening (Found : C, 56·3; H, 8·5. $C_{30}H_{54}O_8N_2S_2$ requires C, 56·7; H, 8·6%). A 1·345% aqueous solution had $[\alpha]_D^{12°}$ + 16·0°, hence $[M]_D^{12°}$ + 101°. Since Graham (J., 1912, **101**, 746) found an average value for the camphorsulphonate ion of 50·0° for a 2% aqueous solution and the D-line, it is clear that no resolution was occurring.

The *dibenzyliodide*, obtained by reaction in cold ethereal solution, formed colourless crystals from alcohol, m. p. 168—169° (Found : C, 45·8; H, 6·0; N, 5·0; I, 43·1. $C_{22}H_{32}N_2I_2$ requires C, 45·7; H, 5·6; N, 4·85; I, 43·9%). This compound, treated in warm aqueous methyl-alcoholic solution with sodium picrate, gave the *dibenzylpicrate*, m. p. 199—201° (Found : N, 14·5. $C_{34}H_{36}O_{14}N_8$ requires N, 14·4%) from alcohol. These two compounds were prepared for comparison with those obtained by the decomposition of the benzyliodide of the octamethyl-base (see Part III).

Hydrogenations.—(1) *Of the dihydrochloride of the " pyro "-base.* A solution of the dihydrochloride (0·367 g.) in water (30 c.c.), mixed with Adams's platinum oxide catalyst (0·019 g.), gave an apparent absorption of 86 c.c. of hydrogen at 20·5° and 757 mm. (*i.e.*, 2·10 mols.) in 1·5 hours. The gases were pumped off through calcium chloride and phosphoric oxide and condensed in a liquid-air trap, where solidification occurred; the excess hydrogen was removed, and the solid product (which melted immediately on removal from the trap) was examined by Dr. G. H. Twigg, who reported :

" The specimen was further purified by distillation from liquid air, and was compared with a number

of hydrocarbons in respect of its vapour pressure at — 78° and relative thermal conductivity. The apparatus used for these tests was the analyser described by Twigg (*Proc. Roy. Soc.*, **1941, 178,** *A*, 106), and is similar to a McLeod gauge with the closed limb dipping into a bath of solid carbon dioxide–acetone. The method of measuring the vapour pressure is described in this paper. The closed limb of the analyser contains a fine wire stretched down the axis of the tube. The voltage required to keep this wire at a constant temperature in the vapour of the substance, the pressure being the vapour pressure at — 78°, is related to the thermal conductivity, and thus to the mass and specific heat of the substance.

" These two tests were applied to the unknown and other hydrocarbons, and the vapour pressure and voltage values obtained are given below. The *n*- and *iso*-butane used were made by hydrogenating Δ^{β}-butene and *iso*butene respectively, and may contain a small quantity, not more than 5%, of unchanged butene.

Substance.	V. p., mm. at −78°.	Conductivity voltage, v.
Unknown	19·2 ± 0·15	1·1215 ± 0·0005
*iso*Butane	19·2 ± 0·1	1·1223 ± 0·0005
n-Butane	9·7	1·0943
Δ^{α}-Butene	13·1	1·0763
trans-Δ^{β}-Butene	8·7	1·0655
cis-Δ^{β}-Butene	6·6	1·0166
Propane *	131	
n-Pentane *	1·38	

* *International Critical Tables*, **1928, 3, 218, 220.** These values are cited only to show the markedly different values given by the immediate homologues.

" From these results, the unknown substance is clearly identified as *iso*butane."

The alcoholic mother-liquor from the above hydrogenation was evaporated to dryness, and the deliquescent residue, recrystallised from alcoholic acetone, gave dimethylamine hydrochloride, m. p. 171° (Found : N, 17·0. Calc. for C_2H_7N,HCl : N, 17·2%). The mother-liquor from the recrystallisation was evaporated, and the residue, shaken with benzenesulphonyl chloride and sodium hydroxide solution, gave benzenesulphondimethylamide, m. p. 48·5—49°, unchanged by admixture with an authentic sample. After allowance for the evolution of 1 mol. of *iso*butane in the above hydrogenation, the total absorption of hydrogen was 3·1 mols. When similar hydrogenations were carried out in organic solvents, *e.g.*, methyl alcohol, some of the *iso*butane remained dissolved in the solvent, and the apparent absorption was therefore between 2 and 3 mols. of hydrogen.

In repetitions of this experiment in which the hydrogenation was stopped when only 1 or 2 mols. of hydrogen had been absorbed, only the hydrochlorides of dimethylamine and of unchanged " pyro "-base could be detected in the solution.

(2) *Of the free " pyro "-base.* A solution of the free base (0·199 g.) in *cyclo*hexane (15 c.c.) containing the catalyst (0·02 g.) underwent very slow hydrogenation which stopped after absorption of 8·4 c.c. of hydrogen during 3·5 hours. Addition of glacial acetic acid (10 c.c.) caused rapid hydrogenation to occur, total absorption of hydrogen being 78·2 c.c. at 18°/758 mm. (*i.e.*, 2·33 mols.). The initial failure may have been due to poisoning of the catalyst by the free base, but more probably indicates a definite difference in reactivity between the base and its salts.

(3) *Of the dimethiodide of the " pyro "-base.* A solution of the dimethiodide (0·308 g.) in methyl alcohol (20 c.c.), with the catalyst (0·018 g.), similarly absorbed 45·0 c.c. of hydrogen at 21°/771 mm. (*i.e.*, 2·62 mols.). The solution on evaporation gave solely crude trimethylamine hydriodide (Found : I, 68·2. Calc. for C_3H_9N,HI : I, 67·9%), which in turn gave the picrate, m. p. 221—222°, and mixed m. p. with an authentic sample, 219—220°. Many repetitions of this experiment were also made in which only 1 or 2 mols. of hydrogen were actually absorbed, but only trimethylamine hydriodide and the unchanged dimethiodide could be detected.

All attempts to reduce an alcoholic solution of the " pyro "-base with sodium failed.

Oxidation.—(1) *By potassium permanganate.* Initial experiments showed that when the dimethochloride of the " pyro "-base was treated in warm sodium carbonate solution with sufficient permanganate to give 2 atoms of oxygen, much unchanged material could be isolated as the picrate, and the solution gave no semicarbazone. When a similar mixture was titrated with permanganate at 70°, oxidation almost ceased when the equivalent of 9·5 atoms of oxygen had been used, and the solution contained oxalic acid. Consequently, the dimethochloride (1·42 g.) and sodium carbonate (4·0 g.) were dissolved in turn in water (240 c.c.) at 70°, and permanganate (6·18 g. ≡ 10 atoms of oxygen) then added. The filtered solution was concentrated, neutralised with dilute sulphuric acid, and evaporated to dryness in a desiccator. The product was repeatedly extracted with boiling ether. The ethereal extracts on evaporation gave oxalic acid, which when crystallised from petrol–ethyl acetate had m. p. 187°, and when then exposed to the air gave the dihydrate, m. p. 101·5° (efferv.), unchanged on mixing with an authentic sample. The residue from the ether extraction, when dissolved in dilute acetic acid and treated with phenylhydrazine, gave bisphenylhydrazine oxalate, m. p. 180° (decomp.; varying with rate of heating), m. p. when mixed with authentic sample of m. p 184° and heated under the same conditions, 183° (Found : C, 54·4; H, 5·9; N, 18·5. Calc. for $C_{12}H_{16}N_4,C_2H_2O_4$: C, 54·9; H, 5·9; N, 18·3%).

In an attempt to isolate the intermediate products, the experiment was repeated, " pyro "-base (0·35 g.), sodium carbonate (1·0 g.), and permanganate (1·30 g. = 5 atoms of oxygen) being used. A portion of the filtered solution, treated with phenylhydrazine, gave the above oxalate; a second portion, treated with excess 1% alcoholic 2 : 4-dinitrophenylhydrazine containing 10% of concentrated hydrochloric acid to prevent separation of the oxalate, gave formaldehyde-2 : 4-dinitrophenylhydrazone; when twice recrystallised from alcohol, this had m. p. 163°, unchanged on admixture with an authentic sample (Found : N, 25·9. Calc. for $C_7H_6N_4O_4$: N, 26·65%).

(2) *By ozone.* A solution of the dimethochloride in water or in acetic acid was unaffected by the passage of ozone for 3 hours. An aqueous solution of the dihydrochloride, when ozonised for 5 hours, underwent decomposition (probably by oxidation of the dimethylamino-groups) but no hydrazone or semicarbazone could be isolated.

Action of Bromine.—A bromine solution (2·24 c.c., 1 mol. Br_2), prepared by mixing bromine (2·50 c.c.) and chloroform (30 c.c.), was added dropwise to one of the " pyro "-base (0·5 g.) in chloroform (10 c.c.). Each drop gave a transient orange precipitate, which rapidly redissolved to a yellow solution; towards the end of the addition, colourless crystals separated and the solution ultimately became colourless. The crystals, when collected and recrystallised from alcohol, had m. p. 239—239·5°, unchanged by admixture with the dihydrobromide of the " pyro "-base (Found : C, 31·4; H, 6·8; Br, 53·4. Calc. for $C_8H_{18}N_2,2HBr$: C, 31·6; H, 6·6; Br, 52·6%). The chloroform filtrate was extracted with dilute hydrochloric acid and the extract warmed with charcoal, an odour of formaldehyde being evolved. The aqueous filtrate, evaporated in a desiccator, gave a brown viscous syrup from which no crystalline compound could be isolated. When this experiment was repeated but with 0·67 mol. of bromine, the same dihydrobromide and unchanged base were isolated. When 2 mols. of bromine were employed, a heavy red oil was immediately precipitated, and on treatment with alcohol this gave the dihydrobromide again. These results contrast markedly with the addition of bromine to a chloroform solution of the octamethyl base, $C(CH_2\cdot NMe_2)_4$, which causes an immediate stable orange precipitate, presumably of a perbromide.

Addition of bromine water to an aqueous solution of the dihydrochloride of the " pyro "-base gave at first a yellow solution, and ultimately an orange precipitate, apparently of a perbromide. [The compound $C(CH_2\cdot NMe_2,HCl)_4$ behaved similarly.] No decolorisation or apparent reaction occurred when methyl-alcoholic solutions of bromine and of the dihydrochloride of the " pyro "-base were mixed; a similar result was obtained when warm acetic acid solutions of bromine and the dimethiodide of the " pyro "-base were mixed.

αγ-Bisdimethylamino-β-methylpropane, $CH_3\cdot CH(CH_2\cdot NMe_2)_2$.—Pure αγ-dibromo-β-methylpropane (33 g.), prepared by Faworski's method (*Annalen*, 1907, **354**, 384), and 30% alcoholic dimethylamine (150 c.c.) were heated together at 130° for 10 hours. The product was diluted with water, neutralised, and ether-extracted to remove neutral impurities; it was then concentrated, basified, and the base extracted with ether and twice distilled. The above *amine* was thus obtained as a colourless liquid (8 g.), b. p. 151—152° (Found : N, 16·8. $C_8H_{20}N_2$ requires N, 19·4%). It gave a *dihydrochloride*, m. p. 233—234° (Found : Cl, 32·4. $C_8H_{20}N_2,2HCl$ requires Cl, 32·7%); a *dimethiodide*, m. p. 267—268° (Found : I, 59·3. $C_{10}H_{26}N_2I_2$ requires I, 59·3%); a dibenzyliodide, obtained as a syrup and as a glass, which could not be purified, but readily gave a *dibenzylpicrate*, m. p. 169—171° (Found : N, 14·6. $C_{34}H_{38}O_{14}N_8$ requires N, 14·4%). These three derivatives were all purified by recrystallisation from alcohol.

All attempts to reduce the dimethiodide catalytically under precisely the same conditions as those employed for the dimethiodide of the " pyro "-base failed.

Synthesis of αγ-Bistrimethylammonium-β-methylpropenylene Di-iodide (XI).—A Grignard reagent prepared from methyl bromide (70 g.) and magnesium (16·6 g., 1·2 atoms) in ether (300 c.c.) was added slowly with stirring and cooling to a suspension of *s*-dichloroacetone (72 g.) in ether (200 c.c.). Next day, the mixture was treated with dilute hydrochloric acid, the ethereal layer removed, the aqueous layer extracted with ether, the ethereal extracts united, concentrated, shaken with sodium bisulphite solution, dried, and distilled. *αγ-Dichloro-β-methylisopropyl alcohol* (VI) was obtained as a colourless liquid (33 g.), b. p. 71—72°/18 mm. (Found : Cl, 49·0. $C_4H_8OCl_2$ requires Cl, 49·7%). A high-boiling residue proved to be a mixture and was disregarded. The carbinol was characterised by boiling with an alcoholic solution of sodium 2-naphthoxide, the *β-hydroxy-β-methyltrimethylene-αγ-bis-2-naphthyl ether* being obtained as colourless crystals from alcohol, m. p. 151—152° (Found : C, 80·2; H, 6·2. $C_{34}H_{32}O_2$ requires C, 80·4; H, 6·1%).

A mixture of the carbinol (VI; 32 g.), dimethylamine (50 g., 4 mols.), and alcohol (100 g.) was heated at 115—125° for 8 hours. The cold product was concentrated, diluted with water, neutralised, extracted with ether to remove non-basic impurities, and the aqueous layer basified and extracted with ether. Fractional distillation gave *αγ-bisdimethylamino-β-methylisopropyl alcohol* (VII; 27 g.), b. p. 80—81°/20 mm. (Found : N, 17·7. $C_8H_{20}ON_2$ requires N, 17·5%); an uninvestigated high-boiling residue remained. This amine gave a *dihydrochloride*, colourless deliquescent crystals from acetone–alcohol (1 : 1 by vol.), m. p. 250° (efferv.) (Found : Cl, 30·3. $C_8H_{20}ON_2,2HCl$ requires Cl, 30·5%); a *dipicrate*, yellow crystals from water, m. p. 172—173° (Found : N, 18·3. $C_8H_{20}ON_2,2C_6H_3O_7N_3$ requires N, 18·1%); and a *dimethiodide*, which crystallised from acetone containing a small quantity of alcohol as a *monohydrate*. The latter on direct heating dissolved

in its water of crystallisation at 105—110°, but on slow heating it became anhydrous between 90° and 120° and then had m. p. 176—177°; confinement in a vacuum over phosphoric anhydride also gave the anhydrous material (Found, for the hydrate: C, 25·8; H, 6·0. $C_{10}H_{26}ON_2I_2,H_2O$ requires C, 26·0; H, 6·1%. Found, for the anhydrous product: C, 27·2; H, 6·2; N, 6·1. $C_{10}H_{26}ON_2I_2$ requires C, 27·0; H, 5·9; N, 6·3%).

Two other syntheses of the amine (VII) were also investigated. It was hoped to convert *s*-dichloroacetone into bisdimethylaminoacetone, $CO(CH_2{\cdot}NMe_2)_2$, and this by the action of methylmagnesium iodide into the amine (VII); the interaction of the dichloroacetone with dimethylamine gave, however, a dark product which could not be distilled or purified. The second method entailed the conversion of αγ-dichlorohydrin into αγ-bisdimethylamino*iso*propyl alcohol, oxidation of the latter to the ketone, and the conversion of this by the Grignard reagent as above into the amine (VII). A mixture of the dichlorohydrin (25 g.), dimethylamine (50 g., 4 mols.), and alcohol (100 g.) was heated in an autoclave at 115—120° for 7 hours. Alcohol and excess dimethylamine were then distilled off, and the residue, when worked up in the usual manner, gave the *αγ-bisdimethylamino*iso*propyl alcohol* as a colourless liquid (16 g.), b. p. 80—82°/17 mm. (Found: N, 18·9. $C_7H_{18}ON_2$ requires N, 19·2%). This amine was characterised as its *dimethiodide*, colourless crystals from alcohol, decomposing at 250° without melting (Found: C, 24·9; H, 5·5; N, 6·5; I, 59·3. $C_9H_{24}ON_2I_2$ requires C, 25·1; H, 5·6; N, 6·5; I, 59·1%). Oxidation of the amino-alcohol to the corresponding ketone could not be achieved, however, and this route to the compound (VII) was not further investigated.

All attempts to dehydrate the amine (VII) by heating with 70% sulphuric acid, powdered potassium hydroxide, or zinc chloride failed. When the dihydrochloride was heated at 260° for 5 mins., some decomposition appeared to occur, but the residue on purification gave the unchanged dihydrochloride (Found: Cl, 30·0%). When, however, the dimethiodide was heated at 185—190° for 10 mins., and the brown syrupy residue then extracted with boiling methyl alcohol until colourless, the insoluble crystalline product, which was unmelted at 350°, proved to be tetramethylammonium iodide (Found: C, 24·6; H, 6·2; N, 6·7; I, 62·4. Calc. for $C_4H_{12}NI$: C, 23·9; H, 6·0; N, 7·0; I, 63·2%).

To prepare the chloro-base (VIII), a solution of thionyl chloride (16 c.c., *ca.* 2 mols.) in chloroform (16 c.c.) was added rapidly with stirring to one of the amine (VII; 16 g.) also in chloroform (80 c.c.). A vigorous reaction caused the clear brown solution to boil and deposit crystals. The mixture was then boiled under reflux for 10 mins., and the chloroform and excess thionyl chloride were removed by distillation. The residue was dissolved in water (25 c.c.), mixed with ether (250 c.c.), and cooled in ice-water whilst a solution of sodium hydroxide (80 g.) in water (160 c.c.) was slowly added with stirring. The ethereal layer was separated, dried, and fractionally distilled, the *β-chloro-αγ-bisdimethylamino-β-methylpropane* (VIII; 12·7 g.) being obtained as a colourless liquid, b. p. 81°/15 mm. (Found: Cl, 19·4. $C_8H_{19}N_2Cl$ requires Cl, 19·9%). This amine gave a *dipicrate*, yellow crystals from alcohol, m. p. 155—156° (Found: N, 17·5. $C_8H_{19}N_2Cl,2C_6H_3O_7N_3$ requires N, 17·6%), and a *dimethiodide* (X), obtained as a brown crystalline material, which, when washed with cold acetone until colourless and then crystallised from alcohol containing a small quantity of water, had m. p. 195—196° (decomp.) (Found: C, 26·3; H, 5·6; N, 6·0. $C_{10}H_{25}N_2ClI_2$ requires C, 25·9; H, 5·4; N, 6·1%). This is very sparingly soluble in boiling absolute alcohol. It is noteworthy that the base (VIII) would not combine with methyl chloride in methyl-alcoholic solution at room temperature.

When this chloro-base (VIII) was boiled with alcoholic potash, potassium chloride was precipitated, but the product was *αγ-bisdimethylamino-β-ethoxy-β-methylpropane* (IX), b. p. 91—92°/15 mm. (Found: N, 14·5. $C_{10}H_{24}ON_2$ requires N, 14·9%), which was characterised as its *dimethiodide*, slightly hygroscopic crystals from a mixture of methyl and ethyl alcohols, melting to a viscous mass between 140° and 150° with effervescence and preliminary softening (Found: C, 30·3; H, 6·7; N, 5·8. $C_{12}H_{30}ON_2I_2$ requires C, 30·5; H, 6·4; N, 5·9%). Several other attempts to eliminate hydrogen chloride from the chloro-base by boiling it with powdered potash or with quinoline all failed. When, however, the dimethiodide (6·2 g.) was added to a boiling solution of pure potassium hydroxide (1 g., 1 mol.) in methyl alcohol (50 c.c.), and the mixture boiled under reflux for 30 mins., elimination of hydrogen chloride occurred smoothly. The precipitated potassium chloride was removed, and the filtrate neutralised with methyl-alcoholic hydrogen chloride, and evaporated to a syrup. This was dissolved in boiling methyl alcohol, and the solution filtered and diluted with alcohol until precipitation of a brown syrup was complete. The latter solidified on standing, and recrystallisation from alcohol gave *αγ-bistrimethylammonium-β-methylpropenylene di-iodide* (XI) as colourless crystals, m. p. 203—204° with darkening and slight preliminary softening (Found: C, 27·9; H, 5·8; N, 6·4; I, 59·6. $C_{10}H_{24}N_2I_2$ requires C, 28·2; H, 5·6; N, 6·6; I, 59·6%). A mixed m. p. determination using equal quantities of this compound and the dimethiodide of the " pyro "-base (m. p. 216—217°) gave 206—210° with darkening and preliminary softening precisely as with the two pure compounds. Since these m. p.'s were affected by both the age of the specimen and the rate of heating, the above values were determined side by side in the same bath with freshly crystallised and dried samples.

The dimethiodide (XI), treated in aqueous solution with sodium picrate, gave the *dimethopicrate*, yellow crystals from hot water, m. p. 245—246° (decomp.) (Found: C, 42·2; H, 4·5; N, 18·2. $C_{22}H_{28}O_{14}N_8$ requires C, 42·0; H, 4·5; N, 17·8%); mixed m. p. with the dimethopicrate of the " pyro "-base (m. p. 257—257·5°), 250—253° (decomp.).

When the dimethiodide (X) of the chloro-base was boiled with excess methyl-alcoholic potash (4 mols.),

decomposition occurred with formation of trimethylammonium iodide, m. p. 254—255° (Found: C, 19·3; H, 5·4; N, 6·9; I, 68·4. Calc. for C_3H_9N,HI: C, 19·3; H, 5·3; N, 7·5; I, 67·9%); prolonged boiling of the original mixture caused the evolution of all the nitrogen as trimethylamine, and the filtrate gave a minute quantity of a red 2 : 4-dinitrophenylhydrazone, m. p. 174—177°. It is probable that the excess potash converted the ion of (X) first into that of (XI), then into (XII), and finally complete elimination of trimethylamine gave an aldehyde which clearly would be unstable in the presence of the hot potash.

Hydrogenation of the Dimethiodide (XI).—(A) A solution of this compound (0·519 g.) in water (25 c.c.), mixed with the platinum catalyst (0·1 g.), gave an apparent absorption of 62·0 c.c. of hydrogen at 17·5°/760 mm. (2·15 mols.), the absorption being rapid and complete. The filtered aqueous solution, evaporated to dryness, gave solely crude trimethylammonium iodide (0·431 g., 95% of theoretical), m. p. 242—245°, raised to 253—254° by warming with acetone and then unchanged by admixture with an authentic sample of m. p. 255—257°. This compound was further identified by conversion into the picrate, m. p. 217—220°, also unchanged by admixture with an authentic sample. The gaseous hydrocarbon evolved during hydrogenation was not analysed, as the source of the dimethiodide (XI) precluded the gas being other than *iso*butane.

(B) A similar reduction was performed in methyl-alcoholic solution to ensure that the *iso*butane remained dissolved and that an accurate measure of the hydrogen absorption was made. The dimethiodide (0·268 g.) in methyl alcohol (40 c.c.) with the catalyst (0·01 g.) absorbed 45·5 c.c. of hydrogen at 20°/761 mm., *i.e.*, 2·96 mols. The filtered solution on evaporation gave trimethylammonium iodide (0·195 g., 91%).

Oxidations.—(A) *Of the dimethiodide* (XI). Solutions of the dimethiodide (1·4 g.) in water (10 c.c.) and of silver sulphate (0·9 g., 1 mol.) in water (100 c.c.) were mixed, filtered, and the filtrate treated at 70° with a solution of potassium permanganate (3·1 g.) and anhydrous sodium carbonate (2 g.) in water (100 c.c.). The mixture was shaken for 10 mins. at this temperature and then filtered, evaporated to 10 c.c., refiltered, and treated with an acetic acid solution of phenylhydrazine. The phenylhydrazine oxalate which separated had, after crystallisation from water, m. p. 182—183°, mixed m. p. with authentic sample, 182—184°.

(B) *Of pyruvic acid.* (*a*) A solution of freshly distilled pyruvic acid (b. p. 70—72°/18 mm., 1·602 g.) and sodium carbonate (5 g.) was similarly treated at 70° with one of potassium permanganate (6·5 g.) in water (200 c.c.). The experiment was then completed precisely as in (A). Yield of phenylhydrazine oxalate, 4·07 g. (73%).

(*b*) A similar oxidation was performed with pyruvic acid (1·532 g.), but the oxalic acid was now precipitated as calcium oxalate and estimated volumetrically. Yield of oxalic acid, 1·470 g. (91%).

It would appear therefore that the oxidation to oxalic acid is not strictly quantitative and some acetic acid may be formed. Oxalic acid itself was found to be unaffected by boiling alkaline permanganate.

Action of Silver Oxide.—(A) *On the dimethiodide of the pyro-base.* The silver oxide used in all these experiments was prepared by interaction of silver nitrate and potassium hydroxide, both in hot aqueous solution; it was collected, washed repeatedly with boiling water, then with alcohol and ether, and dried in a vacuum at room temperature.

A solution of the dimethiodide (8 g.) in water (30 c.c.), mixed with silver oxide (14 g., 3·3 mols. Ag_2O), was boiled for 2 hours, the vapours evolved being absorbed in dilute hydrochloric acid; this was subsequently found to contain trimethylamine (identified as picrate, m. p. 216°) but no other amines or formaldehyde. The main solution was filtered, evaporated in an open dish to half-bulk, cooled, filtered again, and treated with aqueous picric acid. The precipitated *dipicrate* of (XIV) was thrice recrystallised from water and obtained as yellow needles, which were unaffected by exposure to phosphoric anhydride in a vacuum; m. p. 173—174° (Found: C, 44·7; H, 5·25; N, 16·1. $C_{26}H_{34}O_{18}N_8$ requires C, 44·7; H, 4·9; N, 16·0%). Yield of recrystallised picrate, 1 g. Trimethyl*iso*butylammonium picrate has the same m. p. (Hanhart and Ingold, J., 1927, 1017) and almost the same composition; a mixture of the two picrates had, however, m. p. 160—167°.

To identify the ion (XIV) further, the dipicrate was decomposed by hydrochloric acid, the picric acid removed with ether, and the colourless solution concentrated and divided into two portions. (*a*) Excess of chloroauric acid was added to one portion, and the *dichloroaurate* of (XIV), which was immediately precipitated, was collected and, after recrystallisation from dilute acetone, obtained as yellow needles, m. p. 201—202° (Found: for material dried in vacuum over phosphoric anhydride, Au, 42·8; for that dried in a vacuum at 130° for 10 hours, C, 18·5; H, 3·6; N, 3·15; Au, 42·95. $C_{14}H_{30}ON_2Cl_8Au_2$ requires C, 18·2; H, 3·3; N, 3·0; Au, 42·9%). The chloroaurate is sparingly soluble in hot water, readily so in hot acetone.

(*b*) The second portion, similarly treated with chloroplatinic acid, gave the *chloroplatinate* of (XIV), reddish-orange crystals from hot water, m. p. 206—207° (decomp.; efferv.) (Found: for material dried in a vacuum over phosphoric anhydride, Pt, 29·8; for material dried in a vacuum at 130° for 10 hours, C, 25·8; H, 4·7; N, 4·2; Pt, 30·05. $C_{14}H_{30}ON_2Cl_8Pt$ requires C, 25·8; H, 4·6; N, 4·3; Pt, 30·1%). The analytical figures in (*a*) and (*b*) show clearly that the oxygen is not present as a molecule of water of crystallisation.

(B) *On the synthetic dimethiodide* (XI). The dimethiodide (2 g.), water (10 c.c.), and silver oxide (4 g.) were treated precisely as in (A). The dipicrate, similarly recrystallised, had m. p. 173—174°, unchanged by admixture with that from (A) (Found: C, 44·5; H, 5·2; N, 16·2%).

(C) *On the chloro-dimethiodide* (X). (*a*) The dimethiodide (1 g.) in water (10 c.c.), with silver oxide (2·0 g.,

4 mols.), was boiled for 1 hour, and then treated as in (A). The picrate obtained was notably less soluble in hot water than that of (XIV), and after recrystallisation had m. p. 243—246° (decomp.), unchanged by admixture with the synthetic dimethopicrate of m. p. 245—246° (Found: C, 42·6; H, 4·6; N, 18·5%).

(*b*) The experiment was repeated but with 4 g. of silver oxide and 3 hours' boiling. The dipicrate of (XIV) was now obtained, m. p. 173—174°. It is clear, therefore, that small quantities of the oxide merely abstract hydrogen chloride from (X) to give the ion of the synthetic dimethiodide (XI), which then with excess of oxide undergoes the usual degradation to (XIV).

(D) *On an old sample of the "pyro"-base dimethochloride.* This liquid sample (p. 166), similarly treated with silver oxide with limited boiling, also gave the synthetic dimethopicrate, which, thrice recrystallised from water, had m. p. 242—244° (decomp.), unchanged by admixture with authentic sample (Found: C, 42·3; H, 5·1; N, 18·6%).

Both trimethylamine and tetramethylammonium hydroxide were found to be unaffected by boiling in aqueous solution with excess silver oxide for 3 hours.

Acetonyltrimethylammonium picrate, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}NMe_3{\cdot}O{\cdot}C_6H_2(NO_2)_3$, was prepared for comparison with the picrate of (XIV). 30% Aqueous trimethylamine (5 c.c.) was added to a solution of chloroacetone (2 g.) in alcohol (40 c.c.); next day, the solution was evaporated to a syrup and then treated with alcoholic picric acid. The precipitated picrate, recrystallised from alcoholic acetone, formed large yellow needles, m. p. 149—150° (Found: C, 42·3; H, 4·1; N, 16·5. $C_{12}H_{16}O_8N_4$ requires C, 41·9; H, 4·6; N, 16·3%).

Attempted Preparation of 2 : 3-*Bisdimethylamino*-1-*methyl*cyclo*propane*.—For this purpose, 1-methyl*cyclo*propane-*trans*-dicarboxylic acid was required. The synthetic approach from ethyl crotonate (Goss, Ingold, and Thorpe, *loc. cit.*) gave a mixture of the *trans*- and the (*cis*)*cis*-acid, from which the pure *trans*-acid, being present in low proportion, could be isolated only in very small yield. The following experiments were therefore performed with the mixed ethyl esters of the two acids.

Amide. When a mixture of the ester (2 c.c.) and ammonia (30 c.c., *d* 0·88) was shaken for 15 hours and then allowed to evaporate to small bulk at room temperature, white crystals of the crude *amide-ammonium salt*, $C_4H_6(CO{\cdot}NH_2)(CO_2NH_4)$, m. p. 167—169° with effervescence and preliminary softening, separated out (Found: C, 45·5; H, 7·9; N, 17·8. $C_6H_{12}O_3N_2$ requires C, 45·0; H, 7·5; N, 17·5%). The same product was obtained with alcoholic ammonia, and in spite of a wide variation in conditions, a pure diamide could not be isolated.

Hydrazide. When hydrazine hydrate (15 g., 4 mols.) was added with stirring and cooling to a solution of the ester (10 g.) in alcohol (50 c.c.), a white solid was precipitated; recrystallisation of this substance from aqueous alcohol gave only a crude *dihydrazide*, m. p. 167—170°, which could not be further purified (Found: N, 30·4. $C_6H_{12}O_2N_4$ requires N, 32·6%). If the reaction was performed at room temperature, a product of lower nitrogen content, presumably contaminated with the cyclic hydrazide, was obtained. The Curtius degradation was therefore performed on this crude dihydrazide.

Ether (50 c.c.) was added to a solution of the dihydrazide (8·6 g.) in a mixture of water (70 c.c.) and concentrated hydrochloric acid (9 c.c.). The mixture was chilled in ice–salt and stirred whilst a solution of sodium nitrite (7 g.) in water (15 c.c.) was added during 30 mins. A vigorous effervescence of nitrogen finally occurred, and the diazide dissolved in the ether which acquired a pungent odour. The ethereal layer was boiled with alcohol, but a crystalline urethane could not be isolated. The alcoholic solution was evaporated to a syrup, and the latter boiled with hydrochloric aid. The solution on benzoylation furnished 2 : 3-*bisbenzamido*-1-*methyl*cyclo*propane* as colourless needles, m. p. 197—200° (Found: C, 73·5; H, 6·7; N, 9·8. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·4; N, 9·5%). Many other attempts were made to prepare the pure azide, but all failed. Since the major difficulty in this work was clearly the presence of the *cis*-dicarboxylic acid, the conversion of this acid into the *trans*-isomeride was attempted by the method of Buchner (*Annalen*, 1895, **284**, 218), who showed that *cyclo*propane-*cis*-dicarboxylic acid on potash fusion gave a high yield of the *trans*-acid. A similar potash fusion on the mixed methyl-dicarboxylic acids gave, however, a syrupy mixture of acids, apparently consisting mainly of propionic acid. Attempts to synthesise the amine (IV) were therefore abandoned.

Methylation of Trimethyleneimine.—(*a*) A sample of the imine, b. p. 65—70°, reacted vigorously with undiluted methyl iodide, and gave only a sticky product. When ethereal solutions of the base and of excess methyl iodide were mixed at 0°, a white crystalline product slowly separated; two recrystallisations from alcohol gave *trimethyleneimine hydriodide*, m. p. 146·5°, suddenly resolidifying and melting again at 240—250° (decomp.) (Found: C, 20·1; H, 4·4; N, 7·4; ionised I, 68·1. C_3H_8NI requires C, 19·5; H, 4·3; N, 7·6; I, 68·6%).

(*b*) A solution of trimethyleneimine (0·39 g.) in methyl alcohol (5 c.c.) was treated with 15% methyl-alcoholic potash (2·6 c.c., 1 mol. KOH) and then with methyl iodide (2 c.c., 4 mols.) at 0°. After 2 hours the solution was evaporated to dryness on the water-bath, and the product extracted with much boiling ethyl alcohol to remove potassium iodide. The residual white solid, m. p. 225° (decomp., varies with rate of heating), was freely soluble in water, slightly soluble in glycol monomethyl ether, and insoluble in boiling methyl and ethyl alcohol, acetone, chloroform, acetonitrile, and ethyl carbonate. Analysis indicated that it was N-*methyltrimethyleneimine methiodide* still contaminated with a trace of potassium iodide (Found: C, 27·1;

H, 6·15; N, 6·35; ionised I, 60·0. $C_5H_{12}NI$ requires C, 28·2; H, 5·6; N, 6·6; I, 59·6%). This compound was unchanged after boiling with excess methyl iodide for 5 hours.

We are greatly indebted to Dr. G. H. Twigg and Mr. H. S. Peiser for the gas analysis and *X*-ray work, respectively, to Trinity College, Cambridge, for a Rouse Ball Research Studentship (G. M. G.), and to the Department of Scientific and Industrial Research for a grant (A. L.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 23rd*, 1941.]

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29. *The Amino-derivatives of Pentaerythritol. Part III. The Formation and Thermal Decomposition of Some Quaternary Salts of Tetrakisdimethylaminomethylmethane.*

By GEOFFREY M. GIBSON and FREDERICK G. MANN.

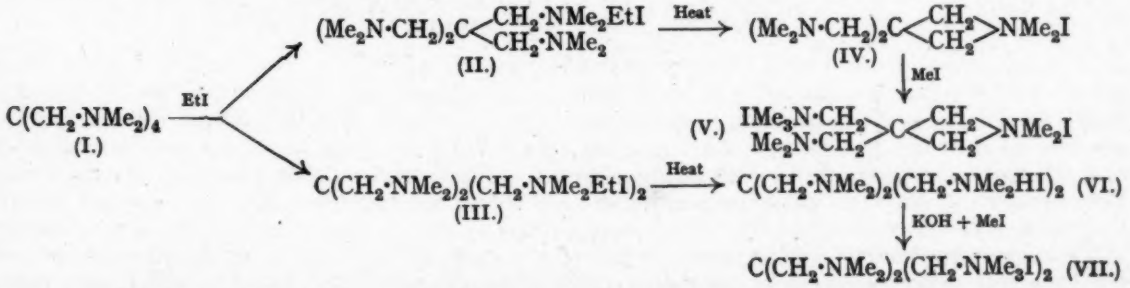
The reaction of this base with methyl iodide has been described in Part I (J., 1938, 1588). It is now shown that the base reacts with ethyl iodide and benzyl iodide to give mixtures of the mono- and bis-quaternary salts, and with allyl iodide to give the monoallyliodide and the allyliodide–hydriodide. Combination with three or four molecules of these alkyl iodides could not be obtained. The thermal decomposition of these compounds has been studied.

The reaction of the base with benzyl iodide in certain circumstances, however, causes rupture of the amine molecule with the formation of dibenzyldimethylammonium iodide and the dibenzyliodide of the " pyro "-base described in Part II (preceding paper).

The mechanism of the above reactions is discussed.

TETRAKISDIMETHYLAMINOMETHYLMETHANE, $C(CH_2{\cdot}NMe_2)_4$, reacts readily with methyl iodide, but even when the latter is in considerable excess, only the dimethiodide is formed; this is unchanged by boiling methyl iodide but on fusion gives the tetramethiodide (Part I; Litherland and Mann, J., 1938, 1588). In view of this abnormal result, the reactions of this octamethyl base with ethyl, allyl, and benzyl iodides have been investigated.

When the octamethyl base (I) is treated with ethyl iodide in the cold, the acetone-soluble monoethiodide (II) is formed; if, however, the original mixture is boiled for a short period and then set aside, the acetone-insoluble, very deliquescent *diethiodide* (III) is formed. No higher ethiodide could be detected. The solubility and instability of the monoethiodide (II) prevented its isolation; its presence was inferred, however, from the fact that when boiled in acetone solution it readily gave ββ-*bisdimethylaminomethyl*-N-*methyltrimethyleneimine monomethiodide* (IV), a compound which is similarly formed also by the decomposition of the monoallyliodide and monobenzyliodide of the base (I) (see below). The

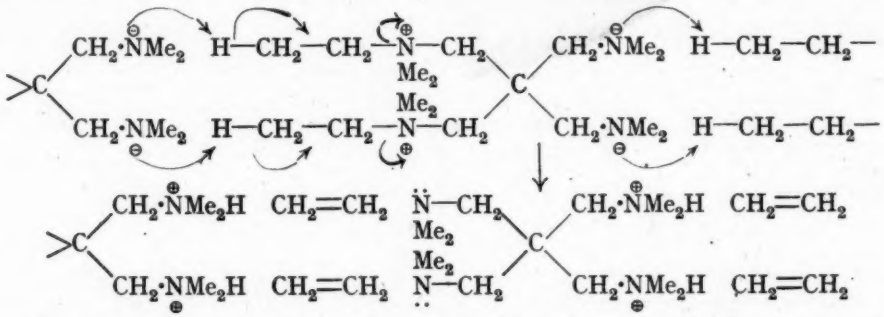


cyclic monomethiodide (IV), when treated with an excess of methyl iodide, combined with only one more molecule, giving the *dimethiodide* (V); apparently the same factors that inhibit the formation of the tetramethiodide of the octamethyl base (I) here inhibit that of the expected trimethiodide.

When the diethiodide (III) was heated, the *dihydriodide* (VI) of the octamethyl base was formed, accompanied by a vigorous evolution of gas, presumably ethylene; the identity of (VI) was confirmed by the fact that when it was treated in turn with potassium hydroxide and methyl iodide, the normal dimethiodide (VII) of the octamethyl base was obtained.

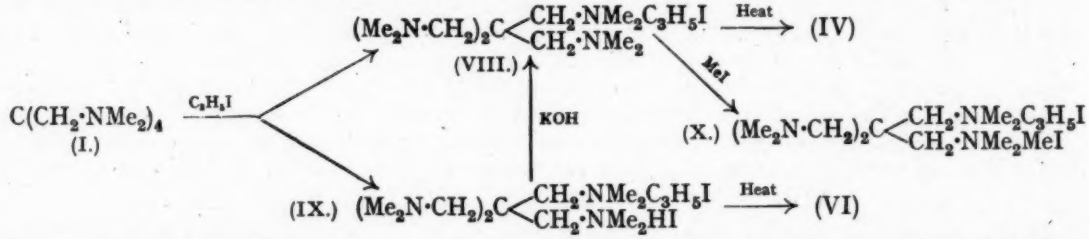
The reason for this marked difference in the thermal decomposition of the diethiodide (III) and the dimethiodide is not far to seek. One of the chief factors in the decomposition of quaternary ammonium hydroxides (and many salts) containing an ethyl group is the elimination of a β-proton from

this ethyl group by the hydroxyl ion, with the formation of ethylene, water, and a tertiary amine (Hanhart and Ingold, J., 1927, 997). A parallel reaction is possible with the diethiodide (III), but now, however, the lone pair of electrons on the two tertiary nitrogen atoms of one molecule will fulfil the function of the hydroxyl ions, and will extract the β-protons from the two ethyl groups of a second molecule. The process will therefore be :



This mechanism explains the formation of the dihydriodide and the evolution of ethylene. The dimethiodide, on the other hand, could clearly give no such reaction, nor by a parallel reaction could the methyl groups split off as methylene radicals and so furnish ethylene, as there is no known example of methyl groups behaving thus during quaternary ammonium decomposition (Hanhart and Ingold, *loc. cit.*); hence the entirely different behaviour of the dimethiodide on heating.

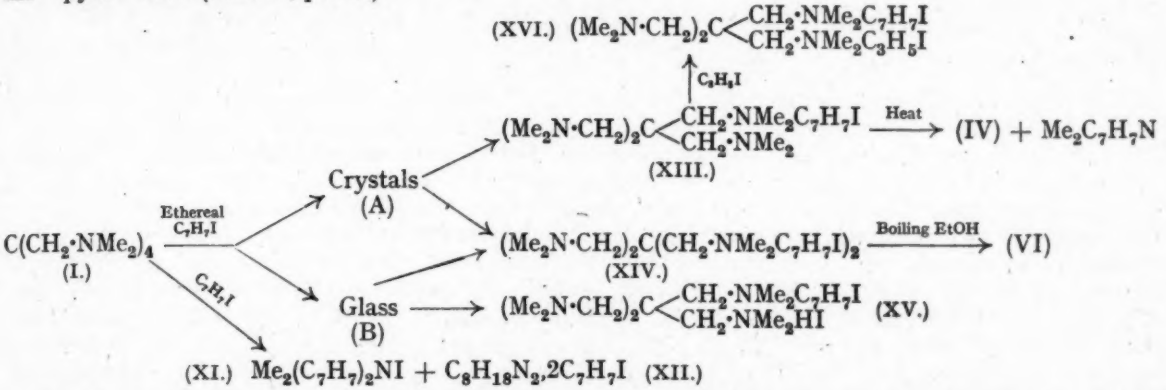
When the octamethyl base (I) was treated with an excess of allyl iodide in the cold, the only products isolated were the acetone-soluble *monoallyliodide* (VIII) and the acetone-insoluble *monoallyliodide monohydriodide* (IX); the constitution of the latter was confirmed by the fact that potassium hydroxide converted it into (VIII). The compound (VIII) on heating passed smoothly over into the cyclic trimethyleneimine compound (IV); when, however, it was treated even with an excess of methyl iodide, only the *monoallyliodide monomethiodide* (X) was formed. The allyliodide hydriodide (IX) on fusion gave the dihydriodide (VI) of the octamethyl base, a reaction similar to that of the diethiodide.



The occurrence of the allyliodide hydriodide (IX) was unexpected, and was not due to the *thermal* decomposition of an intermediate product, since the compound (IX) could be isolated by the use of cold solvents alone. It is possible, however, that a very unstable diallyliodide was formed, and even at room temperature decomposed by a reaction similar to that shown above for the diethiodide but now affecting only one quaternary allylammonium ion. The allyliodide hydriodide (IX) so formed would have greater stability and therefore require heating before the decomposition was repeated with the formation of the dihydriodide (VI). This we regard as the most probable explanation of the formation of the above compounds. Furthermore, the fact that a stable diallyliodide of the octamethyl base does not apparently exist, whereas the diethiodide (III), dibenzyliodide (XIV), and also mixed salts such as the allyliodide–methiodide (X) and the allyliodide–benzyliodide (XVI) (see below) have all been isolated is not unexpected, for von Braun (*Annalen*, 1911, **382**, 5) has shown that in quaternary ammonium decompositions the ease of elimination of groups is allyl > benzyl > ethyl > methyl; clearly, therefore, the diallyliodide should be the least stable of the above bisquaternary salts.

The action of benzyl iodide on the octamethyl base followed that of ethyl and allyl iodides, with certain remarkable differences. When the base and benzyl iodide were mixed with cooling in the absence of a solvent, a pale brown, brittle glass was obtained (cooling was essential, otherwise the considerable heat evolution caused almost complete decomposition of the mixture). The glass was separated by crystallisation from acetone and alcohol into dibenzyldimethylammonium iodide (XI) and the dibenzyliodide of the " pyro "-base (XII) described in Part II, *i.e.*, αγ-bisdimethylamino-β-methylpropene. It

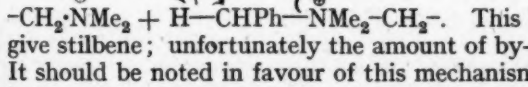
was thought that the iodide (XI) might have been a decomposition product of the compound (XII) arising during extraction or crystallisation of the latter. The compound (XII) could, however, be heated with alcohol or water for long periods without decomposition, and could not, therefore, during its isolation, have furnished the iodide (XI). The reaction which thus produces the benzyliodide of the " pyro "-base is particularly notable owing to the low temperature at which it takes place, in marked contrast to that of 232—233° required to convert the hydrochloride of the octamethyl base into that of the " pyro "-base (Part II, p. 164).



When a mixture of benzyl iodide and the octamethyl base (I) was prepared, however, in chilled ethereal solution, a mixture of crystals (A) and a dark yellow glass (B) was slowly deposited. The crystals were separated into the *monobenzyliodide* (XIII) and the *dibenzyliodide* (XIV) of the octamethyl base; the glass (B) was separated into the dibenzyliodide (XIV) and the *benzyliodide hydriodide* (XV) of this base.

The monobenzyliodide (XIII) on heating behaved similarly to the monoethiodide and monoallyliodide, giving the trimethyleneimine derivative (IV); in this case, however, the other product of the reaction, benzyldimethylamine, was identified, and the complete reaction thus elucidated. It is noteworthy, moreover, that the monobenzyliodide readily united with allyl iodide to give the *monobenzyliodide–allyliodide* (XVI) of the octamethyl base. The previous failure to prepare the diallyliodide, therefore, could not apparently have been due solely to steric factors.

The dibenzyliodide (XIV) also behaved on heating similarly to the diethiodide and diallyliodide in giving the dihydriodide (VI) of the octamethyl base; in this case the reaction occurred very readily, even in boiling alcoholic solution. The benzyliodide hydriodide (XV) is therefore undoubtedly an intermediate stage in this reaction, in which only one of the two quaternary benzyl iodide groups has undergone decomposition; the ease of this decomposition, coming next after that of the allyl derivatives, is in accordance with von Braun's results (*loc. cit.*). It is probable that the mechanism of the conversion of the dibenzyliodide (XIV) into the dihydriodide is similar to that of the diethiodide decomposition, the lone pairs of electrons on the tertiary nitrogen atoms again fulfilling the function of the hydroxyl ion in normal quaternary ammonium hydroxide decomposition: in the present case, however, these lone pairs must split off an α-proton from the benzyl group, with the transient formation of the benzylidene radical, CHPh<, instead of $CH_2{=}CH_2$ as on p. 176, *i.e.*, the essential reaction is now

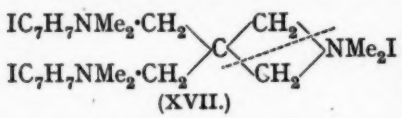


. This being assumed, the benzylidene radicals should unite to give stilbene; unfortunately the amount of by-product isolated was too small for decisive identification. It should be noted in favour of this mechanism, however, that it explains the formation of the dihydriodide (VI), and furthermore, that α-proton attack in quaternary ammonium decompositions, although unusual, will occur if circumstances are favourable. For instance, Ingold and Jessop (J., 1929, 2357) have shown that in the thermal decomposition of fluoryl-9-trimethylammonium hydroxide, the hydroxyl ion removes a proton from the α-carbon atom (the abstraction of a β-proton in this case also being impossible), and the bivalent fluorylidene radicals unite in pairs to form difluorylidene or *oo'*-bisdiphenyleneethylene.

The reason for the formation of dibenzyldimethylammonium iodide (XI) and the dibenzyliodide (XII) of the " pyro "-base when the octamethyl base (I) was treated with excess benzyl iodide in the absence of a solvent is obscure, but may be due to the monobenzyliodide (XIII) of the octamethyl base initially formed undergoing ready decomposition into the trimethyleneimine compound (IV) and benzyl-

dimethylamine. The latter would then unite with benzyl iodide to give (XI), whilst the compound (IV), under the influence of the excess of benzyl iodide, would first give a mono- or di-benzyl derivative such as (XVII) and the latter would then decompose by fission of the ring as described in Part II (p. 167), forming the unstable precursor of the " pyro "-base dibenzyliodide (XII).

It may be objected that this radical cleavage of the molecule (XVII) is unlikely to occur without vigorous heating. It is well known, however, that benzyl groups in quaternary ammonium derivatives have an exceptional lability and that such derivatives in consequence often decompose very much more readily than most other quaternary derivatives (cf. Graymore, J., 1941, 39).



(XVII.)

One striking result emerging from this investigation is that the octamethyl base (I), when treated with an excess of alkyl iodide under normal conditions, apparently never unites with more than 2 mols. of it. Even this formation of a bisquaternary salt occurs readily only with methyl iodide; in the above experiments with ethyl and benzyl iodide the mono- was always formed in much greater yield than the bisquaternary salt, and the addition of the second molecule of alkyl iodide must presumably be much slower than that of the first. Furthermore, only the dimethiodide on heating gave the quadri-quaternary salt, the other dialkyliodides giving the dihydriodide. It was suggested in Part I that this extreme difficulty in forming quadri-quaternary salts was probably partly steric, but was due mainly to increasing energy being required for successive alkyl iodide additions, *i.e.*, these additions changed steadily from exothermic to endothermic reactions. The steric factor is probably a comparatively minor one, since other cases are known where this factor can hardly be present at all; *e.g.*, it has been shown that trimethyl- and triethyltrimethylenetriamine when treated with excess methyl or ethyl iodide, in spite of a vigorous reaction, give only the mono-quaternary salt (Graymore, J., 1938, 1311; Blundell and Graymore, J., 1939, 1787). Phenazine, when treated with methyl sulphate even at 120°, also gives only a mono-quaternary salt (Kehrmann and Havas, *Ber.*, 1913, **46**, 343). Similarly, both isomeric forms of 5 : 10-di-*p*-tolyl-5 : 10-dihydroarsanthren unite with only 1 mol. of methyl iodide, the second arsenic atom remaining persistently 3-covalent (Chatt and Mann, J., 1940, 1184). The electronic explanation of the behaviour of the octamethyl base is probably that the positive pole on one nitrogen atom formed by the union of the first alkyl iodide molecule exerts a marked inductive effect which in turn causes a certain restraint on the lone-electron pairs of the remaining three nitrogen atoms. This restraint hinders but does not prevent the addition of a second alkyl iodide molecule. After this second addition, however, the increased inductive restraint on the lone pairs of the remaining two nitrogen atoms prevents further quaternary-salt formation, except in the case of the methiodides, where a high temperature suffices for this purpose. A similar mechanism can clearly be put forward to account for the behaviour of the above trimethylenetriamine, phenazine, and arsanthren compounds, and, of course, for the fact that the trimethyleneimine methiodide (IV) will unite with only one more molecule of methyl iodide.

Experimental.

Reaction with Ethyl Iodide.—(*a*) A solution of the octamethyl base (I) in ethyl iodide (8 mols.) was boiled under reflux for 15 mins. and then set aside in the dark for 7 days. Some preparations had then deposited colourless crystals of the *diethiodide* (III), which were collected, triturated thoroughly with acetone, and recrystallised from alcohol. Other similar preparations, however, sometimes deposited a dark yellow syrup; in this case, the excess of ethyl iodide was allowed to evaporate at room temperature and the residual syrup was stirred vigorously with acetone, crystallisation of the diethiodide usually occurring at once; sometimes, however, the crude syrup dissolved completely in the acetone, which then slowly deposited the colourless crystals. The diethiodide was thus obtained as very deliquescent crystals, m. p. 128° (Found : N, 9·7; I, 45·3. $C_{17}H_{42}N_4I_2$ requires N, 10·1; I, 45·65%). The acetone washings contained appreciable quantities of the monoethiodide. Unless the base (I) and the ethyl iodide employed in the above preparation are pure, the yellow syrup obtained will not give a crystalline product on treatment with acetone.

(*b*) When, however, the preliminary heating was omitted from otherwise identical experiments, a homogeneous solution was obtained. A test portion, when evaporated and treated with acetone, gave no precipitate of the diethiodide. The main solution, which presumably contained the monoethiodide, was therefore boiled under reflux for 15 mins., evaporated to dryness on the water-bath, and then dissolved in hot acetone. The solution, on standing overnight, deposited a small crop of the slightly impure dihydriodide (VI), m. p. 204—207°, formed apparently by decomposition of traces of the diethiodide. The mother-liquor, after filtration, was then evaporated to dryness, the residue heated on the water-bath for several hours (during which a faint amine odour was evolved), and then recrystallised from acetone, colourless crystals of ββ-*bis-dimethylaminomethyl*-N-*methyltrimethyleneimine monomethiodide* (IV), m. p. 206·5—207·5°, being deposited; a mixture of these crystals with those of the dihydriodide (VI) had m. p. 181—185°. Further successive

crops of (IV) were obtained by repeating the evaporation of the acetone mother-liquor to dryness, followed by heating and recrystallisation as before. The united crops, when recrystallised from alcohol, gave the pure monomethiodide (IV), m. p. 208—208·5° (decomp.) (Found: C, 41·0; H, 8·3; N, 12·5; I, 38·4. $C_{11}H_{26}N_2I$ requires C, 40·4; H, 8·0; N, 12·8; I, 38·8%). The identity of (IV) as a methiodide and not a hydriodide was confirmed by the fact that ether extracted no amine from a mixture of (IV) with concentrated aqueous potash.

When a mixture of the monomethiodide (IV) and of methyl iodide was boiled under reflux for 6 hours, and the excess of methyl iodide then evaporated, the residue, after extraction with cold acetone, consisted of much unchanged monomethiodide and the corresponding dimethiodide (V). This residue, when recrystallised from alcohol, furnished the monomethiodide. Dilution of the alcoholic mother-liquors with acetone caused crystallisation of the *dimethiodide*, which, when washed with acetone and recrystallised from alcohol, separated as the *dihydrate*, m. p. 123—124° (decomp.; efferv.) (Found: N, 8·1; I, 50·8. $C_{12}H_{30}N_2I_2,2H_2O$ requires N, 8·3; I, 50·3%).

Thermal Decomposition of the Diethiodide (III).—The carefully dried diethiodide was plunged into an oil-bath at 128°, and the temperature was then increased to 135—140° and kept thereat for 20 mins., by which time effervescence had ceased and a reddish-brown syrup remained. Addition of acetone to a solution of this syrup in a minimum of alcohol caused separation of a pale brown solid, which was recrystallised from alcohol, washed with acetone until colourless, and again recrystallised. The *monohydrated dihydriodide* (VI) of the octamethyl base was thus obtained, m. p. 208—209° (Found: C, 29·9; H, 6·8; N, 11·0; I, 49·3. $C_{13}H_{34}N_4I_2,H_2O$ requires C, 30·1; H, 7·0; N, 10·8; I, 49·0%). The identity of this compound was confirmed by saturating its aqueous solution with potassium hydroxide and then extracting it with ether. Evaporation of the ether gave an oil which rapidly combined with methyl iodide to give the dimethiodide of the octamethyl base, m. p. 145—146°, unchanged by admixture with an authentic sample.

Reaction with Allyl Iodide.—Allyl iodide (4 mols.) was slowly added to the octamethyl base (I) with stirring and ice-water cooling, and the mixture set aside in the dark overnight. The viscous product was well stirred with a small quantity of cold acetone; the latter was then decanted and on keeping (particularly if diluted with ethyl acetate) deposited the pure *monoallyliodide* (VIII) of the octamethyl base as colourless crystals which on heating melted with effervescence at 145—146°, then resolidified and melted again with effervescence at 207°, these values being unchanged after recrystallisation from alcoholic ethyl acetate (Found: C, 46·5; H, 9·1; N, 13·6; I, 30·7. $C_{16}H_{37}N_4I$ requires C, 46·6; H, 9·0; N, 13·6; I, 30·8%).

The sticky insoluble residue from the acetone extraction, when vigorously triturated with fresh acetone, ultimately solidified, giving thus crystals of the *monoallyliodide monohydriodide* (IX), m. p. 153—154°; these, when triturated afresh with alcohol and acetone and then recrystallised from alcohol, gave the pure salt (IX), m. p. 157—158° (Found: C, 35·4; H, 7·0; N, 10·5; I, 46·2. $C_{16}H_{37}N_4I,HI$ requires C, 35·6; H, 7·0; N, 10·4; I, 47·0%). It is clear from the above results that the compound (IX) must be formed during the original reaction and at room temperature, and did not arise when the products of this reaction were in contact with hot solvents.

A 0·86% methyl-alcoholic potassium hydroxide solution (6·0 c.c., *i.e.*, slightly less than 1 mol. of KOH) was added to a suspension of the hydriodide (IX; 0·5 g.) in methyl alcohol. The clear solution was evaporated to dryness at room temperature, extracted with cold acetone to remove a trace of unchanged material, and the acetone solution filtered and evaporated. The residue, when recrystallised from alcoholic ethyl acetate, furnished the monoallyliodide (VIII), melting with effervescence at 145—146°, and resolidifying and finally remelting at 207—208°, these values being unchanged by admixture with an authentic sample.

Thermal Decompositions.—(a) *Of the monoallyliodide* (VIII). The substance was heated at 160—165° for a few minutes, during which an amine odour was evolved. The residue, which solidified on cooling, was washed with acetone until colourless, and thus furnished the pure trimethyleneimine compound (IV), m. p. 210—210·5°, unchanged by admixture with previous specimens (Found: I, 39·1%).

(b) *Of the allyliodide hydriodide* (IX). The hydriodide was heated at 170—175° for 15 mins. An alcoholic solution of the brown, sticky residue was diluted with acetone, and the colourless needles which separated were recrystallised from alcohol, furnishing the dihydriodide (VI), m. p. and mixed m. p. 210·5—211·5° (Found: I, 48·5%).

A mixture of the monoallyliodide (VIII) and methyl iodide was boiled under reflux for 4 hours, and the excess of methyl iodide then evaporated: the residue, after thorough washing with acetone, furnished the pure and very deliquescent *monoallyliodide monomethiodide* (X), m. p. 114—115° (decomp., efferv.), unchanged by recrystallisation from alcohol (Found: N, 9·8; I, 46·0. $C_{17}H_{40}N_4I_2$ requires N, 10·1; I, 45·8%). When a thoroughly dry sample of this compound was plunged into an oil-bath at 115—120° and kept at this temperature for 30 mins., a sharp odour, unlike that of an aliphatic amine, was first evolved, followed by that of an amine itself. The viscous, pale brown residue, when mixed with alcohol, gave colourless crystals in small yield; these were purified by adding water to their suspension in boiling alcohol until a clear solution was obtained. Cooling gave crystals, which when thoroughly dried did not melt below 355° and were apparently the tetramethiodide of the octamethyl base (I); the small amount available made identification uncertain (Found: C, 24·6; H, 6·1; N, 7·5; I, 61·4. Calc. for $C_{17}H_{44}N_4I_4$: C, 25·1; H, 5·45; N, 6·9; I, 62·5%). When an aqueous solution of this compound was treated with potassium hydroxide (1 mol.) and then evaporated

to dryness and thoroughly extracted with alcohol to remove any potassium iodide, the N : I ratio in the residue was still 1 : 1; hence the above compound could not have been the trimethiodide hydriodide, $C(CH_2 \cdot NMe_2)_4, 3CH_3I, HI$.

Reaction with Benzyl Iodide.—(1) The base (I) (5 g.) was chilled in ice-water, and freshly prepared benzyl iodide (10·5 c.c., 4 mols.) slowly added. The mixture was vigorously shaken to prevent crystallisation of the benzyl iodide, and the corked flask containing the mixture returned to the ice-water and there set aside for six days, during which the mixture rapidly became gelatinous, and ultimately set to a hard, pale reddish-brown glass, which when gently warmed melted to a viscous liquid. (*a*) A portion of this glass was dissolved in boiling water, and the solution, after spontaneous cooling and filtration from a slight gummy deposit, gave on stirring colourless crystals of dibenzyldimethylammonium iodide (XI), m. p. after recrystallisation from water, 191—192° (Found : C, 54·6; H, 6·0; N, 4·0; I, 36·2. Calc. for $C_{16}H_{20}NI$: C, 54·5; H, 5·7; N, 4·0; I, 36·1%). Emde (*Arch. Pharm.*, 1909, **247**, 355) gives m. p. 191°. (*b*) An alcoholic solution of a second portion slowly deposited a cream-coloured, crystalline powder, m. p. 162—164°, which on further alcoholic crystallisation gave colourless crystals of the dibenzyliodide (XII) of the " pyro "-base, m. p. 168—169°, unchanged by admixture with an authentic sample (Found : N, 4·7; I, 44·1. Calc. for $C_{22}H_{32}N_2I_2$: N, 4·85; I, 43·9%). The identity of this compound was further confirmed by conversion into the dibenzyl-picrate, m. p. 199—201°, also unchanged by admixture with a known sample (Found : N, 14·45. Calc. for $C_{34}H_{36}O_{14}N_8$: N, 14·4%). An aqueous solution of (XII) was kept at 100° for 2·5 hours, and the unchanged compound (XII), m. p. 166°, then crystallised; a similar result was obtained in hot alcoholic solution. It is clear, therefore, that in the above preparation the compound (XI) could not have arisen by decomposition of (XII). (*c*) The main bulk of the original glass was now dissolved in much boiling acetone, which on cooling and standing for 2 days slowly deposited small, pale yellow crystals. These were collected and washed with acetone until colourless, and were now only slightly soluble in boiling acetone; either the solubility of this compound had originally been increased by the presence of other substances (a common occurrence in this investigation) or, less probably, the compound had been formed in the hot acetone solution. The colourless crystals, twice recrystallised from alcohol, gave the pure dibenzyliodide (XII), m. p. and mixed m. p. 168—169°. The alcoholic mother-liquors, on spontaneous evaporation, deposited these colourless crystals and also large, very pale yellow crystals of the iodide (XI), m. p. 191—192°, mixed and unmixed.

(2) When, however, the above quantities of the base (I) and benzyl iodide, each now dissolved in ether (20 c.c.), were mixed with ice-cooling, and the mixture set aside for 24 hours in the dark, a crystalline solid (A) separated, and a hard glassy film (B) remained attached to the walls of the flask. The crystals (A) were collected, washed with ether, and dissolved in a minimum of hot acetone–ethyl acetate (1 : 1 by vol.); after 24 hours a small crop of the colourless crystalline *monohydrate* of the *dibenzyliodide* (XIV), m. p. 128—129° (efferv.), unchanged by recrystallisation from alcohol, was collected (Found : C, 46·6; H, 7·3; N, 7·9; I, 36·5. $C_{27}H_{46}N_4I_2,H_2O$ requires C, 46·4; H, 6·9; N, 8·0; I, 36·4%). The acetone–ethyl acetate mother-liquor, chilled in ice, then deposited a larger crop of the pure *monobenzyliodide* (XIII), m. p. 146—147° (with resolidification and remelting at 190—196°), unchanged by recrystallisation from ethyl acetate containing a trace of alcohol (Found : C, 51·8; H, 8·4; N, 12·3. $C_{20}H_{39}N_4I$ requires C, 51·9; H, 8·4; N, 12·1%). It is noteworthy that the compound (XIV) is only slightly, and the compound (XIII) readily, soluble in cold acetone.

The glass (B), when boiled with acetone containing a small quantity of alcohol, was converted into colourless crystals, which, washed with acetone and dried, had m. p. 139—145°. These were boiled with sufficient alcohol to dissolve about half the material. The insoluble portion, recrystallised from much alcohol, gave the *benzyliodide hydriodide* (XV) of the octamethyl base, m. p. 170° (Found : C, 39·7; H, 7·0; N, 9·5; I, 42·8. $C_{30}H_{42}N_4I_2$ requires C, 40·6; H, 6·8; N, 9·5; I, 43·0%). The alcoholic mother-liquor slowly deposited crystals which were again fractionally extracted with hot alcohol; the latter extract, filtered and cooled, deposited the hydrated dibenzyliodide (XIV), m. p. 128—128·5° after further recrystallisation (Found : N, 7·7; I, 36·1%). Further quantities of (XIV) were also slowly deposited from the alcoholic acetone with which the glass (B) had originally been treated.

Thermal Decompositions.—(a) *Of the monobenzyliodide* (XIII). This compound, heated at 150—155° for 5 mins., gave a mixture of a liquid and a crystalline solid which, when washed in turn with ether and acetone, furnished the trimethyleneimine compound (IV); this, after crystallisation from alcohol, had m. p. and mixed m. p. 209—210° (Found : I, 39·3%). The ethereal extract reacted readily with methyl iodide to give benzyltrimethylammonium iodide, m. p. 177—178° after recrystallisation from alcoholic ethyl acetate (Found : I, 45·7. Calc. for $C_{10}H_{16}NI$: I, 45·8%). Emde (*loc. cit.*) gives m. p. 179°.

(b) *Of the dibenzyliodide* (XIV). An alcoholic solution of (XIV) was boiled under reflux for 6 hours, the solvent removed, and the syrupy residue dissolved in hot acetone. Cooling gave colourless crystals of the dihydriodide (VI), which, after being washed with acetone and recrystallised from alcohol, had m. p. and mixed m. p. 212—213°.

A concentrated acetone solution of the monobenzyliodide (XIII), to which excess of allyl iodide had been added, was set aside in the dark for 3 days. The crystalline *monobenzyliodide–allyliodide* (XVI) was then collected and washed with acetone; m. p. 145—146° (efferv.) unchanged by recrystallisation from alcohol (Found : C, 43·2; H, 7·3; N, 8·9. $C_{23}H_{44}N_4I_2$ requires C, 43·8; H, 7·0; N, 8·9%).

All the compounds isolated in this investigation were dried overnight in a vacuum over phosphoric anhydride,

and the hydrates recorded must clearly have considerable stability. It is noteworthy that many alkyl halides of the octamethyl base (I) possess m. p.'s which, although sharp, vary considerably with the rate of heating. All mixed m. p.'s were therefore determined side by side with the original material.

We express our indebtedness to Trinity College for a Rouse Ball Research Studentship (G. M. G.).

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 23rd,* 1941.]

30. *The Active Principles of Leguminous Fish-poison Plants. Part VI. Robustic Acid.*

By STANLEY H. HARPER.

A substance isolated from the ethereal extract of *Derris robusta* has been shown to be a monocarboxylic acid, $C_{27}H_{24}O_8$ (less probably $C_{28}H_{26}O_8$), containing two methoxyl groups, to which the name *robustic acid* has been given. It is probably related to lonchocarpic acid, $C_{26}H_{26}O_6$, a monocarboxylic acid containing one methoxyl group isolated by Jones (*J. Amer. Chem. Soc.*, 1934, **56**, 1247) from a species of *Lonchocarpus*, as they both give the same sequence of colour changes in the Durham test.

IN the course of examination of various plant materials for their insecticidal activity several species of *Derris* and *Derris* products have been tested. Among these was a colourless crystalline substance isolated from the ethereal extract of *Derris robusta* and forwarded by Dr. S. Krishna of the Forest Research Institute, Dehra Dun, India. Although this substance was non-toxic to *Aphis rumicis* (the bean aphis), a chemical examination has been made as far as the limited amount of material would allow.

The substance separated from the ethereal extract of *D. robusta* and crystallised from acetone or alcohol contained methoxyl groups but did not give a blue colour in the Durham test (see footnote, J., 1939, 1100). It was optically inactive in acetone or benzene solution. These properties are closely in accord with those of tephrosin, but, although the substance did not give a ferric chloride colour, it dissolved in aqueous potassium hydroxide to give a sparingly soluble potassium salt, from which the original material was recovered on acidification. Confirmation of its acidic properties was obtained by shaking an ethereal suspension with 5% sodium carbonate solution; the material slowly dissolved in the aqueous layer and could be recovered by acidification. This substance is therefore regarded as a carboxylic acid and the name *robustic acid* is proposed.

Analyses of robustic acid and of derivatives described subsequently for carbon and hydrogen do not distinguish between $C_{27}H_{24}O_8$ and $C_{28}H_{26}O_8$ for robustic acid and corresponding formulæ differing by CH_2 for the derivatives. The methoxyl contents, corresponding to two methoxyl groups in robustic acid, are more closely in accord with the formulæ with less carbon atoms, but the evidence is not sufficiently conclusive to enable a decision to be made. Analysis of the *potassium* salt shows the acid to be a monocarboxylic acid. Esterification in benzene with diazomethane gave the *methyl* ester. Attempts to show the presence of a keto-group by oximation were unsuccessful, but in view of the difficulty of oximating rotenone this cannot be regarded as proof of the absence of a keto-group. Catalytic hydrogenation to *dihydrorobustic acid* shows the presence of one double bond, and the slow rate of reduction suggests this to be cyclic (cf. the ease of reduction of rotenone with that of elliptone).

That the titration of robustic acid in hot alcohol, which leads to conflicting results, is not a true neutralisation, as it is in aqueous solution, is shown by the non-recovery of the acid on acidification; no definite products have so far been obtained.

Prior to this there has been only one instance of an acid being reported from *Derris* or *Lonchocarpus* species. This material, lonchocarpic acid, $C_{26}H_{26}O_6$, m. p. 201°, a monocarboxylic acid containing one methoxyl group, was isolated by Jones (*J. Amer. Chem. Soc.*, 1934, **56**, 1247) from an unknown species of *Lonchocarpus* from Venezuela. Through the kindness of Dr. H. A. Jones it has been possible to make a comparison of the two substances. Both behave similarly in the Durham test but in marked contrast to rotenone and toxicarol.

Because of their closely related origin and their similarity of behaviour in the Durham test it is thought that robustic and lonchocarpic acids are related both to each other and to rotenone, but from a consideration of their formulæ there does not appear to be any simple relationship between them. Robustic acid is not the methoxy-homologue of lonchocarpic acid, since this would necessitate a formula, $C_{27}H_{28}O_7$, which is ruled out by the analytical figures.

It is hoped to continue the investigation of robustic acid when more favourable conditions occur.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. Methoxyl determinations are by the author, using Clark's semimicro-method (*J. Assoc. Off. Agric. Chem.*, 1932, **15**, 136). Melting points are uncorrected.

Robustic acid crystallised from acetone or alcohol in colourless elongated prisms, m. p. 190°. Qualitative tests showed the absence of nitrogen, halogens, and sulphur (Found: C, 68·4, 68·5; H, 5·1, 5·1; OMe, 13·1, 13·2; *M*, Rast, 496, 451. $C_{27}H_{24}O_8$ requires C, 68·1; H, 5·1; 2OMe, 13·0%; *M*, 477. $C_{28}H_{26}O_8$ requires C, 68·6; H, 5·3; 2OMe, 12·7%; *M*, 491. $C_{27}H_{28}O_7$ requires C, 69·8; H, 6·1; 2OMe, 13·4%).

Titration in hot alcohol with sodium hydroxide gave a sharp end-point, but in excess of the theoretical value, and on acidification the acid was not recovered (53·65 mg. required 7·05 c.c. of 0·02N-sodium hydroxide. Calc., 5·62 c.c.).

By shaking the acid in ethereal suspension with 5% aqueous potassium hydroxide, immediate solution resulted, followed shortly by separation of the sparingly soluble *potassium* salt in colourless plates (50·0 mg. on ignition gave 7·4 mg. of potassium sulphate. Found: equiv. 550). The silver salt decomposed on drying.

Oxidation with iodine in alcohol in the presence of sodium acetate gave no recognisable product (cf. the formation of dehydrorotenone from rotenone). Robustic acid could not be methylated with methyl sulphate and alkali, but in one experiment, in which the reaction mixture was left overnight, a small quantity of substance, m. p. 167°, was obtained, insoluble in alkali. In the Durham test it gave the same sequence of colour changes as the acid, but the quantity was too small to permit further investigation (Found: OMe, 16·9%).

Esterification with diazomethane in benzene gave the *methyl* ester, which crystallised from chloroform–alcohol in plates, m. p. 190°, was insoluble in potassium hydroxide, and gave a marked depression of m. p. with robustic acid. In the Durham test the ester gave a brown colour with nitric acid, followed by a crimson colour on addition of ammonia (Found: C, 68·7; H, 5·3; OMe, 19·6. $C_{28}H_{26}O_8$ requires C, 68·6; H, 5·3; 3OMe, 19·0. $C_{29}H_{28}O_8$ requires C, 69·0; H, 5·6; 3OMe, 18·4%).

Robustic acid (250 mg.) was hydrogenated in ethyl acetate (20 c.c.) in the presence of platinum oxide (50 mg.). Absorption was slow, but a sharp break occurred corresponding to 1 mol. of hydrogen. After filtration and evaporation, the residue crystallised from alcohol to give oblique elongated parallelepipeds of *dihydrorobustic acid* (212 mg.), m. p. 180° (Found: C, 68·2, 68·0; H, 5·8, 5·8; OMe, 13·2. $C_{27}H_{26}O_8$ requires C, 67·8; H, 5·5; 2OMe, 13·0%. $C_{28}H_{28}O_8$ requires C, 68·3; H, 5·8; 2OMe, 12·6%). The crystals had a marked violet fluorescence. Esterification in benzene with ethereal diazomethane gave the *methyl* ester, which crystallised from chloroform–alcohol in prisms, m. p. 207—208° (Found: C, 68·85; H, 6·0; OMe, 20·0. $C_{28}H_{28}O_8$ requires C, 68·3; H, 5·5; 3OMe, 19·0%. $C_{29}H_{30}O_8$ requires C, 69·2; H, 6·0; 3OMe, 18·4%). Both this and the previous ester showed a tendency to give high values for methoxyl.

Durham test: The following sequence of colour changes was observed:

	HNO_3 ⟶		NH_3 ⟶
Robustic acid		green	red
Lonchocarpic acid		green	red
Toxicarol		red	green
Rotenone		red	blue

I am indebted to Dr. S. Krishna for the robustic acid, to Dr. H. A. Jones for the sample of lonchocarpic acid, and to the Ministry of Agriculture and the Colonial Development Fund for grants which have made this work possible.

Rothamsted Experimental Station, Harpenden, Herts. [*Received, November 22nd*, 1941.]

NOTES.

Some Derivatives of β-o-*Methoxyphenylpropaldehyde.* By A. Zaki and H. Fahim.

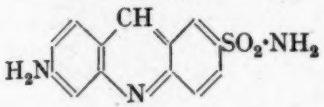
β-*o*-Methoxyphenylpropionyl chloride was obtained from β-*o*-methoxyphenylpropionic acid and thionyl chloride as a slightly yellow, fuming liquid with a penetrating odour, b. p. 165°/40 mm. It was identified by conversion into the amide, m. p. 110—111° (Buck, *J. Amer. Chem. Soc.*, 1932, **54**, 3663; Slotta and Heller, *Ber.*, 1930, **63**, 3037).

β-o-*Methoxyphenylpropaldehyde.*—A well-stirred boiling solution of the preceding chloride in dry xylene was hydrogenated in presence of palladium. The sodium bisulphite compound of β-*o*-methoxyphenylpropaldehyde, m. p. 163—164°, separated in white feathery crystals when a portion of the xylene solution was immediately shaken with sodium bisulphite solution and left over-night. β-o-*Methoxyphenylpropaldehyde-p-nitrophenylhydrazone*, obtained by treating another portion of the xylene solution with *p*-nitrophenylhydrazine, separated from dilute alcohol in yellow crystals, m. p. 126—127° (Found: C, 64·5; H, 5·7; N, 14·0. $C_{16}H_{17}O_3N_3$ requires C, 64·2; H, 5·7; N, 14·3%). β-*o*-Methoxyphenylpropaldehyde, liberated on treatment of the sodium bisulphite derivative with alkali, had b. p. 260° (micro).

Attempts to prepare benzpyrans from these compounds by digestion with hydriodic acid were unsuccessful. —The Egyptian University, Cairo. [*Received, November 1st*, 1941.]

2-Aminoacridine-7-sulphonamide. By ERIC AARONS and ADRIEN ALBERT.

IT is well known that benzenesulphonamide acquires chemotherapeutic value only when an amino-group is inserted in the *p*-position. The acridine nucleus displays its full antiseptic effect only when an amino-group is inserted in the 2- or the 5-position (Albert, Rubbo, and Goldacre, *Nature*, 1941, **147**, 332, 709). In response to a request from Dr. Malcolm Manifold of the Department of Biochemistry, Oxford University, we have combined these structural features in one molecule by effecting the synthesis of *2-aminoacridine-7-sulphonamide* (I).



(I.)

Preparation of 2-Nitroacridone-7-sulphonamide.—2-Nitroacridone-7-sulphonyl chloride (Matsumura, *J. Amer. Chem. Soc.*, 1938, **60**, 593) (45 g.) was finely powdered and suspended in acetone (1 l.), and dry ammonia passed in at the rate of 3 bubbles a second for an hour, with stirring and cooling. The precipitated sulphonamide was ground under acetone (250 ml.), collected, and dried at 120°. Yield, 31 g. of a yellow solid that was purified by dissolution in warm water (500 ml.) containing sodium hydroxide (10 g.), filtration, and precipitation with a slight excess of ammonium chloride.

Reduction to 2-Aminoacridine-7-sulphonamide (I).—A suspension of finely powdered 2-nitroacridone-7-sulphonamide (12 g.) in alcohol (600 ml.) was refluxed while sodium amalgam (430 g. of 2½%) was added during 2 hours. Refluxing was continued for 2 hours longer, a rapid stream of carbon dioxide as well as vigorous stirring being maintained throughout. After distillation of the alcohol from a water-bath, the residue was separated from the mercury and washed with warm water (2 portions of 500 ml.). The white solid that remained (2-aminodihydroacridine-7-sulphonamide) was boiled for 10 minutes with water (600 ml.), concentrated hydrochloric acid (10 ml.), and ferric chloride (20 g.). After cooling in ice, the hydrochloride of *2-aminoacridine-7-sulphonamide* crystallised in red needles; it was recrystallised from 50 parts of water, the corresponding aminoacridinesulphonic acid, formed during the reduction, remaining undissolved. The yield was 40%. The free base formed yellow-orange crystals from 3,500 parts of boiling water and was more soluble in acetone and alcohol. M. p. 253° (sealed tube, decomp.) (Found: C, 53·5; H, 4·5; N, 14·5; loss on drying at 120°, 6·0. $C_{13}H_{11}O_2N_3S,H_2O$ requires C, 53·6; H, 4·5; N, 14·4; H_2O, 6·2%). The substance dissolves in sodium hydroxide solution with a yellow colour and is precipitated by ammonium chloride. Its strength as an acid is similar to and its strength as a base is stronger than that of sulphanilamide.

To lessen hydrolysis during reduction, recourse was had to the aluminium amalgam method of Albert and Ritchie (*J. Soc. Chem. Ind.*, 1941, **60**, 102). Although successful from this point of view, the method presented the difficulty of eluting the product from the alumina on which it was tenaciously adsorbed.

2-Aminoacridine-7-sulphonic Acid.—The above aluminium amalgam method satisfactorily reduced 2-nitroacridone-7-sulphonic acid to 2-aminoacridine-7-sulphonic acid. No adsorption difficulties were encountered. Sodium 2-nitroacridone-7-sulphonate (30 g.) (Matsumura, *loc. cit.*) was dissolved in boiling water (1500 ml.) and aluminium foil (15 g.), amalgamated as required by dipping into alcoholic mercuric chloride solution (5%) and washing with alcohol, was added during ¾ hour; thereafter boiling was continued for ¼ hour. The alumina was separated and washed with four portions of boiling water (each of 250 ml. containing 50 ml. of concentrated aqueous ammonia). The united filtrates were made acid to Congo-paper with hydrochloric acid and treated, while boiling, with ferric chloride (about 3 g.) until a permanent blue spot test was given with potassium ferrocyanide. The suspension was made alkaline, and the liquid filtered from ferric hydroxide, concentrated to 50 ml., and made acid with hydrochloric acid. Yield, 75% of orange crystals with the properties described by Matsumura. The product did not combine with acids in aqueous solution.

An alternative synthesis of 2-aminoacridine-7-sulphonamide was attempted by acetylating the sodium salt of the above acid and converting it through the sulphonyl chloride into 2-acetamidoacridine-7-sulphonamide, However, on treatment of the latter with sodium hydroxide, sodium 2-acetamidoacridine-7-sulphonate was re-formed, and hydrolysis with boiling hydrochloric acid was slow and led to extensive resinification.—UNIVERSITY OF SYDNEY. [*Received, December 8th*, 1941.]

Periodic Acid as a Test for the Constitution of Polysaccharides. By VINCENT C. BARRY, THOMAS DILLON, and WINIFRED MCGETTRICK.

IN recent years it has been discovered that certain polysaccharides, on methylation and subsequent hydrolysis, yield 2 : 4 : 6-trimethyl hexoses, from which it is inferred that in these compounds, unlike starch and cellulose, the third carbon atom of each hexose unit is engaged in linking that unit with the first carbon atom of a neighbouring unit. In this group of compounds are included a polyglucose contained in the cell membrane of yeast (Zechmeister and Toth, *Biochem. Z.*, 1934, **270**, 309), a polygalactose contained in agar-agar (Percival and Somerville, J., 1937, 1615), and laminarin contained in laminariæ (Barry, *Sci. Proc. Roy. Dublin Soc.*, 1939, **22**, 56).

A simple confirmatory test for the constitution of these polysaccharides is afforded by periodic acid, a reagent introduced into polysaccharide chemistry by Jackson and Hudson (*J. Amer. Chem. Soc.*, 1937, **59**, 2049). Periodic acid reacts with the group $\equiv C(OH)—C(OH)\equiv$, splitting the carbon bond and oxidising each

C·OH to CHO (Clutterbuck and Reuter, J., 1935, 1467). In any polysaccharide in which the linkage of the units is 1 : 4, the necessary pair of adjacent C·OH groups is provided by carbon atoms 2 and 3; if, however, carbon atom 3 takes part in the linkage of the units, then no pair of adjacent C·OH groups is available and such a polysaccharide should not be attacked by periodic acid. This note gives an account of the application of this test to two of the three polysaccharides mentioned above, laminarin and agar-agar.

For the sake of comparison with the polysaccharides, the action of periodic acid on 3-methyl methylglucoside was examined. 3-Methyl glucose was prepared by the method of Freudenberg and Hixon (*Ber.*, 1923, **56**, 2125) and was converted into the methylglucoside by Fischer's method (Irvine and Scott, J., 1913, **103**, 573). The syrupy product had $[\alpha]_D$ +101° (c = 4·15) (Irvine and Scott's preparation had $[\alpha]_D$ +99·3°, c = 1·973). The syrup (0·793 g.) was treated with 0·269M-periodic acid (32 c.c.). Immediately after making up, the rotation of this solution was +3·91° (l = 2). It was unchanged after 24 hours. In the meantime a considerable quantity of iodine had separated, showing that periodic acid had been reduced. At the end of the experiment 0·673 g. of syrup was recovered from the solution. This syrup did not reduce Fehling's solution and had $[\alpha]_D$ +99·9°. The constancy of the rotatory power and the recovery of 85% of the syrup apparently unchanged would point to the conclusion that the periodic acid did not act on the 3-methyl methylglucoside; but that the appearance of iodine was due to the action of the reagent on some optically inactive impurities in the syrup. In the oxidation of starch and of cellulose no free iodine is produced, from which it would appear that in the oxidation of two neighbouring C·OH groups periodic acid is not reduced to hydriodic acid. When α-methylglucoside (1·24 g.) was left standing with the same solution of periodic acid (50 c.c.), the rotation fell from +7·55° to +5·25° in 1 hour and to +5·15° in 18 hours.

In the first experiments with laminarin, iodine was also produced. When, however, the laminarin was purified by repeated deposition from water (see Barry, *Sci. Proc. Roy. Dublin Soc.*, 1938, **21**, 615) no free iodine appeared, and the results referred to later were obtained.

During the course of these experiments it was found that the expensive periodic acid could be effectively replaced by sodium paraperiodate. This salt can be easily prepared by oxidising a hot solution of iodine in sodium hydroxide with chlorine (Partington, "Text-Book of Inorganic Chemistry," Macmillan and Co., 5th edn., p. 372). It dissolves readily in dilute sulphuric acid and, for our purposes at least, the presence of sodium and sulphate ions is not objectionable. The course of the reaction may be readily followed by titration of the free iodine formed by the addition of potassium iodide to the solution (Clutterbuck and Reuter, *loc. cit.*). The procedure was to add a standard solution of the paraperiodate in an equivalent quantity of dilute sulphuric acid to the solid polysaccharide and to withdraw 0·25 c.c. from time to time for titration. As a control, cellulose, in the form of absorbent cotton and of filter-paper, was treated in the same way. (The rate of oxidation of starch is much too rapid for this purpose.) A typical series of results is shown in the table:

Time, hours.	Absorbent cotton.†	Filter-paper.†	Agar.*	Lamin-arin.†	Time, hours.	Absorbent cotton.†	Filter-paper.†	Agar.*	Lamin-arin.†
24	4·08	4·08	8·02	4·08	168	3·50	3·44	7·96	3·94
48	3·90	3·90	7·88	4·04	240	3·46	3·38	8·00	3·92
72	3·74	3·80	7·86	4·00	312	3·38	3·30	8·00	3·88
120	3·58	3·60	7·96	3·98	648	3·20	3·13	—	3·73

* 1 G. of agar with 40 c.c. of 0·47M-periodic acid.

† 1 G. of polysaccharide with 40 c.c. of 0·235M-periodic acid.

The figures under each polysaccharide represent the number of c.c. of N/10-thiosulphate required to titrate the iodine liberated on addition of potassium iodide and sulphuric acid to 0·25 c.c. of the solution. Diminution in the figure thus represents oxidation of the polysaccharide.

The small diminution in the figures for laminarin during the first 240 hours is within the limit of experimental error. In other experiments with the same substance this diminution was not apparent. After 240 hours, however, a definite diminution begins to take place. This may be due to a slow action of the oxidising agent on terminal glucose units. At the end of the experiment the cellulose and the laminarin were hydrolysed and treated with phenylhydrazine acetate. No glucosazone was obtained from either the cotton or the filter-paper, whereas it was obtained in plenty from the laminarin.

No figure is available for the agar at 648 hours. At the end of 47 days, however, the titration had fallen to 7·68, showing that at the end of this long contact with the reagent some kind of oxidation was just beginning.

This remarkable stability of agar towards periodic acid is interesting from several points of view. From methylated agar, in addition to 2 : 4 : 6-trimethyl *d*-galactose, Forbes and Percival (J., 1939, 1844) have isolated 2 : 4-dimethyl 3 : 6-anhydro-*l*-galactose (by remethylation of the products of hydrolysis) and they believe that the anhydro-sugar pre-exists in the polysaccharide. The invulnerability of agar to periodic acid supports this view, since, if the 3 : 6-anhydrogalactose were an artefact produced from galactose units in which carbon atom 3 did not take part in the linkage, such galactose units would present $=C(OH)—C(OH)=$ units for attack. According to the figures of Forbes and Percival, 13% of the galactose would then be vulnerable and an appreciable reduction of periodic acid would take place.

On the other hand, Pirie (*Biochem. J.*, 1936, **30**, 369) obtained hepta-acetyl *dl*-galactose by acetylation of

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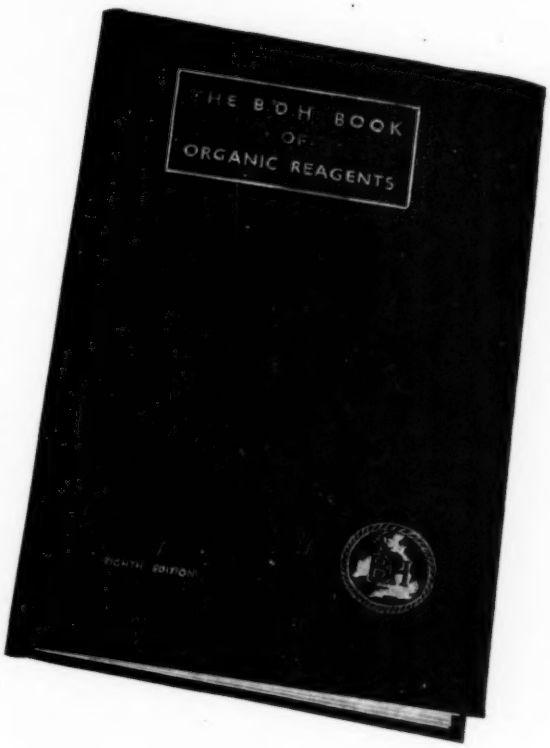

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